



STIC Search Report

Biotech-Chem Library

STIC Database Tracking Number: 149953

TO: Dwayne C Jones
Location: 3b87 / 3c70
Wednesday, April 06, 2005
Art Unit: 1614
Phone: 571-272-0578
Serial Number: 10 / 761096

From: Jan Delaval
Location: Biotech-Chem Library
Remsen 1a51
Phone: 571-272-22504
jan.delaval@uspto.gov

Search Notes

Jones, Dwayne

149953

From: Chan, Christina
Sent: Monday, April 04, 2005 6:08 PM
To: Jones, Dwayne; STIC-Biotech/ChemLib
Subject: RE: RUSH

Please rush. Thanks Chris

Chris Chan
TC 1600 New Hire Training Coordinator and SPE 1644
(571)-272-0841
Remsen, 3E89

-----Original Message-----

From: Jones, Dwayne
Sent: Monday, April 04, 2005 12:46 PM
To: Chan, Christina
Subject: FW: RUSH

Christina,

I believe that you can approve RUSH searches, if not sorry (who does?). Could you approve of this RUSH request for me please?

Dwayne

-----Original Message-----

From: Jones, Dwayne
Sent: Monday, April 04, 2005 12:43 PM
To: Richter, Johann
Subject: RUSH

Johann,

I have a late Reissue, 10/761,096, that needs an action by this Friday, could you please approve a RUSH for this application? Thanks in advance.

Dwayne

http://expoweb1:8001/cgi-bin/expo/GenInfo/pnquery.pl?PAT_ID=5336691

WEST Search History

[Hide Items](#)[Restore](#)[Clear](#)[Cancel](#)

DATE: Wednesday, April 06, 2005

Hide?	<u>Set</u> <u>Name</u>	<u>Query</u>	<u>Hit</u> <u>Count</u>
		<i>DB=PGPB,USPT; PLUR=YES; OP=OR</i>	
<input type="checkbox"/>	L7	L6 or l5	71
<input type="checkbox"/>	L6	L4 and l1	31
<input type="checkbox"/>	L5	\$6tramadol near5 ((phenacetin or acetaminophen) or (\$6acetamino near4 phenol))	53
<input type="checkbox"/>	L4	L3 and l2	475
<input type="checkbox"/>	L3	(phenacetin or acetaminophen) or (\$6acetamino near4 phenol)	6655
<input type="checkbox"/>	L2	\$6tramadol	1035
<input type="checkbox"/>	L1	(514/629,646,649,650)![CCLS]	2183

END OF SEARCH HISTORY

20577

149953
Access DB#

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Dwight C. Jones Examiner #: 70299 Date: 05 APR 05
Art Unit: 614 Phone Number: 301-205-77 Serial Number: 10/761,696
Mail Box and Bldg/Room Location: (3270 and 3637) KEMSEN Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: see attached sheet

Inventors (please provide full names): _____

Earliest Priority Filing Date: 06 SEP 91

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

1- ~~Also please do~~
~~a litigation search too.~~
LAW
4-5-05

2- Please search claims 6
and 16

CS- ~~part~~ ~~then~~

STAFF USE ONLY

Searcher: Jan
Searcher Phone #: 22504
Searcher Location: _____
Date Searcher Picked Up: 4/6/05
Date Completed: 4/6/05
Searcher Prep Review Time: _____
Critical Prep Time: 15
Online Time: 10

Type of Search

NA Sequence (#) _____
AA Sequence (#) _____
Structure (#) _____
Bibliographic ✓
Litigation _____
Fulltext _____
Patent Family _____
Other _____

Vendors and cost where applicable

STN ✓
Dialog _____
Questel/Orbit _____
Dr. Link _____
Lexis/Nexis _____
Sequence Systems _____
WWW/Internet _____
Other (specify) _____

=> d his

(FILE 'HOME' ENTERED AT 07:06:24 ON 06 APR 2005)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 07:06:33 ON 06 APR 2005

E TRAMADOL/CN
L1 1 S E3
E C16H25NO2/MF
L2 149 S E3 AND (46.150.18 AND 46.150.1)/RID
L3 4 S L2 AND TRAMADOL
L4 29 S L2 AND CYCLOHEXANOL AND DIMETHYLAMINO AND METHOXYPHENYL
L5 25 S L4 NOT L1,L3
L6 13 S L5 AND 3 METHOXYPHENYL
SEL RN 4 5 13
L7 3 S E1-E3
L8 7 S L1,L3,L7
SEL RN
L9 71 S E4-E10/CRN
E ACETAMINOPHEN/CN
L10 1 S E3
L11 395 S C8H9NO2/MF AND 46.150.18/RID AND 1/NR
L12 66 S L11 AND HYDROXYPHENYL
L13 36 S L12 AND ACETAMIDE
L14 24 S L13 AND 4
L15 1 S L10 AND L14
SEL RN
L16 325 S E1/CRN
L17 2 S L9 AND L16
L18 69 S L9 NOT L17
L19 43 S L18 AND (MXS/CI OR COMPD OR WITH)
L20 26 S L18 NOT L19
L21 301 S L16 AND (MXS/CI OR COMPD OR WITH)
L22 2 S L21 AND C16H25NO2
L23 2 S L17,L22
L24 24 S L16 NOT L21

FILE 'HCAPLUS' ENTERED AT 07:23:11 ON 06 APR 2005

L25 15 S L23
L26 2 S L25 AND (RAFFA R? OR VAUGHT J?)/AU
L27 1 S L25 AND (ORTHO? OR MCNEIL? OR MC NEIL?)/PA,CS
L28 1 S L25 AND (PY<=1991 OR PRY<=1991 OR AY<=1991)
L29 2 S L26-L28
L30 1058 S L8 OR L20
L31 1144 S TRAMADOL OR U26255A OR U() (26255A OR 26255 A OR 26 255A OR 26
L32 17 S 2 DIMETHYLAMINO METHYL 1 3 METHOXYPHENYL CYCLOHEXANOL
L33 1 S 2() (DIMETHYL OR DIMETHYL OR DI METHYL OR DIME) ()AMINO METHYL
L34 45 S TRAMAL OR CG315 OR CG 315
L35 1198 S L30-L34
L36 11440 S L15 OR L24
L37 7018 S ACETAMINOPHEN? OR TYLENOL
L38 98 S (4 OR P OR PARA) () (HYDROXYPHENYL OR HYDROXY PHENYL) ()ACETAMID
L39 4876 S PARACETAMOL
L40 15 S 4() (ACETYLAMINO OR ACETYL AMINO) () PHENOL
L41 463 S (4 OR P) ()ACETAMIDOPHENOL
L42 404 S (4 OR P) () (HYDROXYACETANILIDE OR HYDROXY ACETANILIDE)
L43 63 S ABENSANIL OR ACAMOL OR ACENOL OR ACETAGESIC OR ACETALGIN OR A
L44 368 S CLARATAL OR CLIXODYNE OR CROCIN# OR DAFALGAN# OR DAPHALGAN# O
L45 175 S FEBROGESIC OR FEBRO GESIC OR FEBROLIN# OR FENDON# OR FEPANIL#
L46 4951 S NEBS OR NOBEDON# OR NSC109028 OR NSC() (109028 OR 109 028) OR
L47 990 S PARALEN# OR PARAMOL? OR PARASPEN# OR PARELAN# OR PARMOL OR PA
L48 8 S TABALGIN# OR TACHIPIRINA OR TAPAR OR TEMLO OR TEMPANAL OR TEM
L49 11 S ACETYL(1W) (HYDROXYANILINE OR HYDROXY ANILINE)

L50 327 S ACETYLAMINOPHENOL OR ACETYL AMINOPHENOL OR ACETYL AMINO PHENO
L51 1563 S ACETANILIDE(L)HYDROXY
L52 372 S ACETYL(1W) (AMINOPHENOL OR AMINO PHENOL)
L53 16899 S L36-L52
L54 201 S L35 AND L53
L55 6 S L54 AND (RAFFA ? OR VAUGHT ?)/AU
L56 5 S L54 AND (ORTHO? OR MCNEIL? OR MC NEIL?)/PA,CS
L57 9 S L55,L56
L58 8 S L57 NOT PSOAS/TI
L59 12 S L54 AND (PY<=1991 OR PRY<=1991 OR AY<=1991)
L60 10 S L59 NOT L29,L58
SEL DN AN 1 2
L61 2 S L60 AND E2-E7
L62 10 S L29,L58,L61
L63 10 S L62 AND L25-L62
L64 4 S L63 AND TRAMADOL(S) (HCL OR HYDROCHLORIDE)
L65 10 S L63,L64
SEL RN

FILE 'REGISTRY' ENTERED AT 07:51:18 ON 06 APR 2005

L66 192 S E8-E199
L67 2 S L66 AND L23
L68 6 S L66 AND L8,L9
L69 17 S L66 AND L15,L16
L70 10 S L66 AND L24
L71 6 S L69 NOT L15,L70
L72 5 S L71 NOT 330988-71-1
L73 19 S L67,L68,L70,L72
L74 173 S L66 NOT L73
L75 8 S L74 AND (46.150.18 AND 46.150.1)/RID
SEL RN 2-6
L76 5 S E200-E204
L77 24 S L73,L76

FILE 'HCAPLUS' ENTERED AT 07:57:05 ON 06 APR 2005

L78 10 S L77 AND L65
L79 94 S L76
L80 1124 S ?TRAMADOL?
L81 194 S L79,L80 AND L53
L82 10 S L81 AND (PY<=1991 OR PRY<=1991 OR AY<=1991)
L83 6 S L82 NOT L78
L84 10 S L78 AND L25-L65,L78-L83
SEL HIT RN

FILE 'REGISTRY' ENTERED AT 07:58:51 ON 06 APR 2005

L85 25 S E205-E229

=> fil reg

FILE 'REGISTRY' ENTERED AT 07:59:12 ON 06 APR 2005

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

COPYRIGHT (C) 2005 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 5 APR 2005 HIGHEST RN 847968-12-1

DICTIONARY FILE UPDATES: 5 APR 2005 HIGHEST RN 847968-12-1

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

 *
 * The CA roles and document type information have been removed from *
 * the IDE default display format and the ED field has been added, *
 * effective March 20, 2005. A new display format, IDERL, is now *
 * available and contains the CA role and document type information. *
 *

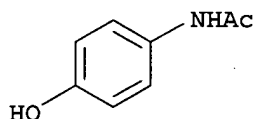
Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:

<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> d ide can tot l85

L85 ANSWER 1 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
 RN 209967-51-1 REGISTRY
 ED Entered STN: 16 Aug 1998
 CN Acetamide, N-(4-hydroxyphenyl)-, magnesium salt (2:1) (9CI) (CA INDEX NAME)
 MF C8 H9 N O2 . 1/2 Mg
 SR CA
 LC STN Files: CA, CAPLUS, USPATFULL
 CRN (103-90-2)



● 1/2 Mg

Hit compounds
 for references
 1-10, set L84,
 pages 30-68

4 REFERENCES IN FILE CA (1907 TO DATE)
 4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

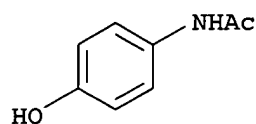
REFERENCE 1: 135:14351

REFERENCE 2: 134:33001

REFERENCE 3: 132:54898

REFERENCE 4: 129:113538

L85 ANSWER 2 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
 RN 209967-50-0 REGISTRY
 ED Entered STN: 16 Aug 1998
 CN Acetamide, N-(4-hydroxyphenyl)-, monocation salt (9CI) (CA INDEX NAME)
 MF C8 H9 N O2 . Cs
 SR CA
 LC STN Files: CA, CAPLUS, USPATFULL
 CRN (103-90-2)



● Cs

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 135:14351

REFERENCE 2: 134:33001

REFERENCE 3: 132:54898

REFERENCE 4: 129:113538

L85 ANSWER 3 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN

RN 209967-48-6 REGISTRY

ED Entered STN: 16 Aug 1998

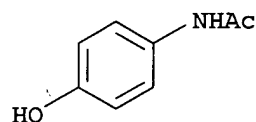
CN Acetamide, N-(4-hydroxyphenyl)-, monolithium salt (9CI) (CA INDEX NAME)

MF C8 H9 N O2 . Li

SR CA

LC STN Files: CA, CAPLUS, USPATFULL

CRN (103-90-2)



● Li

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 135:14351

REFERENCE 2: 134:33001

REFERENCE 3: 132:54898

REFERENCE 4: 129:113538

L85 ANSWER 4 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN

RN 209967-47-5 REGISTRY

ED Entered STN: 16 Aug 1998

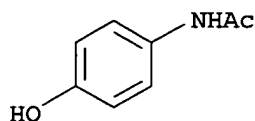
CN Acetamide, N-(4-hydroxyphenyl)-, calcium salt (2:1) (9CI) (CA INDEX NAME)

MF C8 H9 N O2 . 1/2 Ca

SR CA

LC STN Files: CA, CAPLUS, USPATFULL

CRN (103-90-2)



● 1/2 Ca

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 135:14351

REFERENCE 2: 134:33001

REFERENCE 3: 132:54898

REFERENCE 4: 129:113538

L85 ANSWER 5 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN

RN 209967-46-4 REGISTRY

ED Entered STN: 16 Aug 1998

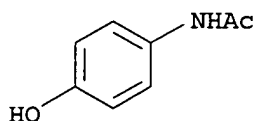
CN Acetamide, N-(4-hydroxyphenyl)-, monolithium salt, hexahydrate (9CI) (CA INDEX NAME)

MF C8 H9 N O2 . 6 H2 O . Li

SR CA

LC STN Files: CA, CAPLUS, USPATFULL

CRN (103-90-2)



● Li

● 6 H₂O

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 134:33001

REFERENCE 2: 132:54898

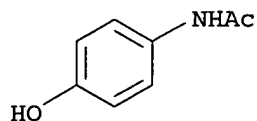
REFERENCE 3: 129:113538

L85 ANSWER 6 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN

RN 209967-45-3 REGISTRY

ED Entered STN: 16 Aug 1998

CN Acetamide, N-(4-hydroxyphenyl)-, calcium salt (2:1), dihydrate (9CI) (CA
INDEX NAME)
MF C8 H9 N O2 . 1/2 Ca . H2 O
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (103-90-2)



● 1/2 Ca

● H₂O

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 134:33001

REFERENCE 2: 132:54898

REFERENCE 3: 129:113538

L85 ANSWER 7 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN

RN 209967-44-2 REGISTRY

ED Entered STN: 16 Aug 1998

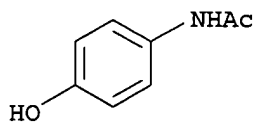
CN Acetamide, N-(4-hydroxyphenyl)-, monosodium salt, heptahydrate (9CI) (CA
INDEX NAME)

MF C8 H9 N O2 . 7 H2 O . Na

SR CA

LC STN Files: CA, CAPLUS, USPATFULL

CRN (103-90-2)



● Na

● 7 H₂O

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 134:33001

REFERENCE 2: 132:54898

REFERENCE 3: 129:113538

L85 ANSWER 8 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN

RN 209967-42-0 REGISTRY

ED Entered STN: 16 Aug 1998

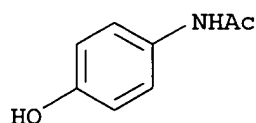
CN Acetamide, N-(4-hydroxyphenyl)-, monosodium salt, hexahydrate (9CI) (CA INDEX NAME)

MF C8 H9 N O2 . 6 H2 O . Na

SR CA

LC STN Files: CA, CAPLUS, USPATFULL

CRN (103-90-2)



● Na

● 6 H₂O

3 REFERENCES IN FILE CA (1907 TO DATE)

3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 134:33001

REFERENCE 2: 132:54898

REFERENCE 3: 129:113538

L85 ANSWER 9 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN

RN 148229-79-2 REGISTRY

ED Entered STN: 22 Jun 1993

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1S,2S)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1S-cis)-

OTHER NAMES:

CN (-)-(1S,2S)-Tramadol hydrochloride

CN (-)-Tramadol

CN E 381

FS STEREOSEARCH

DR 194224-67-4

MF C16 H25 N O2 . Cl H

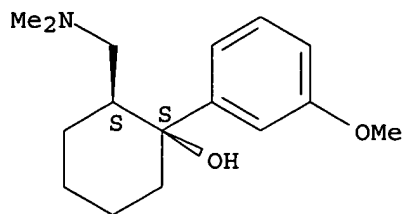
CI COM

SR CA

LC STN Files: ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS, CHEMCATS, CIN, EMBASE, MEDLINE, PROMT, SYNTHLINE, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

CRN (123134-25-8)

Absolute stereochemistry. Rotation (-).



● HCl

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

46 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
46 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:190982
REFERENCE 2: 141:401084
REFERENCE 3: 141:130
REFERENCE 4: 140:399213
REFERENCE 5: 139:191276
REFERENCE 6: 139:143236
REFERENCE 7: 139:106588
REFERENCE 8: 138:100762
REFERENCE 9: 137:288205
REFERENCE 10: 136:299735

L85 ANSWER 10 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN

RN 148229-78-1 REGISTRY

ED Entered STN: 22 Jun 1993

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1R,2R)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1R-cis)-

OTHER NAMES:

CN (+)-Tramadol

CN (+)-trans-Tramadol hydrochloride

CN E 382

FS STEREOSEARCH

MF C16 H25 N O2 . Cl H

CI COM

SR CA

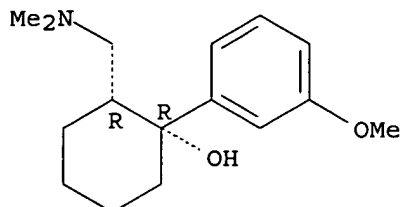
LC STN Files: ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS,

CASREACT, CHEMCATS, EMBASE, MEDLINE, PROMT, SYNTHLINE, TOXCENTER,
USPAT2, USPATFULL

(*File contains numerically searchable property data)

CRN (123154-38-1)

Absolute stereochemistry. Rotation (+).



● HCl

48 REFERENCES IN FILE CA (1907 TO DATE)

48 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:190982

REFERENCE 2: 141:401084

REFERENCE 3: 141:130

REFERENCE 4: 140:399213

REFERENCE 5: 140:368032

REFERENCE 6: 139:159829

REFERENCE 7: 139:143236

REFERENCE 8: 139:106588

REFERENCE 9: 138:100762

REFERENCE 10: 137:190754

L85 ANSWER 11 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN

RN 148218-19-3 REGISTRY

ED Entered STN: 22 Jun 1993

CN Phenol, 3-[(1S,2S)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-,
hydrochloride (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Phenol, 3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, hydrochloride,
(1S-cis)-

OTHER NAMES:

CN (-)-O-Desmethyltramadol hydrochloride

CN EM 724

FS STEREOSEARCH

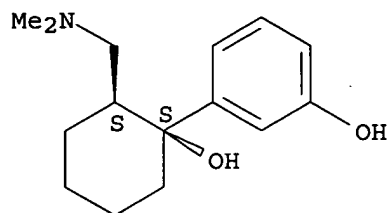
MF C15 H23 N O2 . Cl H

SR CA

LC STN Files: CA, CAPLUS, CHEMCATS, USPAT2, USPATFULL

CRN (144830-15-9)

Absolute stereochemistry. Rotation (-).



● HCl

10 REFERENCES IN FILE CA (1907 TO DATE)
10 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:36331
REFERENCE 2: 131:67592
REFERENCE 3: 127:292994
REFERENCE 4: 127:190519
REFERENCE 5: 126:171384
REFERENCE 6: 126:84457
REFERENCE 7: 126:69971
REFERENCE 8: 121:212995
REFERENCE 9: 119:80214
REFERENCE 10: 119:20350

L85 ANSWER 12 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN

RN 147731-80-4 REGISTRY

ED Entered STN: 25 May 1993

CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with (1R-cis)-3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]phenol (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Phenol, 3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, (1R-cis)-, mixt. contg. (9CI)

FS STEREOSEARCH

MF C15 H23 N O2 . C8 H9 N O2

CI MXS

SR CA

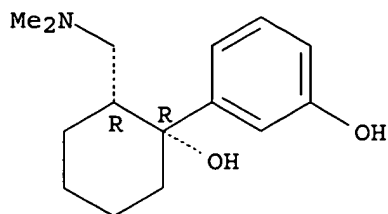
LC STN Files: CA, CAPLUS

CM 1

CRN 144830-14-8

CMF C15 H23 N O2

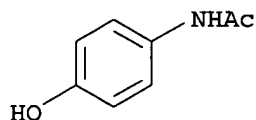
Absolute stereochemistry. Rotation (+).



CM 2

CRN 103-90-2

CMF C8 H9 N O2



1 REFERENCES IN FILE CA (1907 TO DATE)

1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 118:261016

L85 ANSWER 13 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN

RN 147731-79-1 REGISTRY

ED Entered STN: 25 May 1993

CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with (1S-cis)-3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]phenol (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Phenol, 3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, (1S-cis)-, mixt. contg. (9CI)

FS STEREOSEARCH

MF C15 H23 N O2 . C8 H9 N O2

CI MXS

SR CA

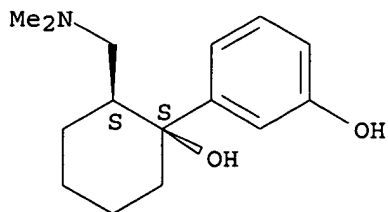
LC STN Files: CA, CAPLUS

CM 1

CRN 144830-15-9

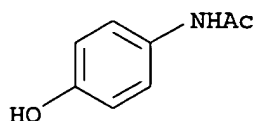
CMF C15 H23 N O2

Absolute stereochemistry. Rotation (-).



CM 2

CRN 103-90-2
CMF C8 H9 N O2



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 118:261016

L85 ANSWER 14 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN 147657-25-8 REGISTRY
ED Entered STN: 20 May 1993
CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with cis-2-
[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)cyclohexanol (9CI) (CA
INDEX NAME)

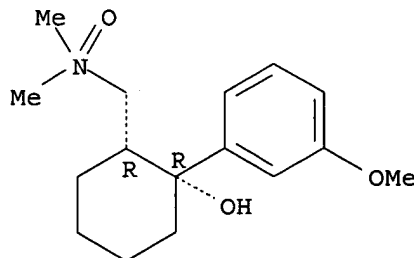
OTHER CA INDEX NAMES:

CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with cis-(±)-2-
[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol N-oxide
CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with cis-(±)-2-
[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)cyclohexanol
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, N-oxide,
cis-(±)-, mixt. contg.
CN Cyclohexanol, 2-[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)-,
cis-(±)-, mixt. contg.
CN Cyclohexanol, 2-[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)-, cis-,
mixt. contg. (9CI)
FS STEREOSEARCH
MF C16 H25 N O3 . C8 H9 N O2
CI MXS
SR CA
LC STN Files: CA, CAPLUS

CM 1

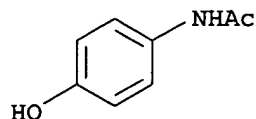
CRN 147441-56-3
CMF C16 H25 N O3

Relative stereochemistry.



CM 2

CRN 103-90-2
CMF C8 H9 N O2



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 118:261016

L85 ANSWER 15 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN

RN 147630-10-2 REGISTRY

ED Entered STN: 19 May 1993

CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with cis-(+)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, cis-(+)-, mixt. contg.

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, cis-, mixt. contg. (9CI)

OTHER NAMES:

CN Acetaminophen-tramadol hydrochloride mixt.

FS STEREOSEARCH

MF C16 H25 N O2 . C8 H9 N O2 . Cl H

CI MXS

SR CA

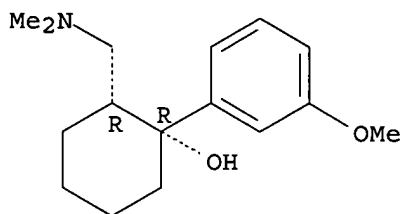
LC STN Files: CA, CAPLUS

CM 1

CRN 36282-47-0 (27203-92-5)

CMF C16 H25 N O2 . Cl H

Relative stereochemistry.

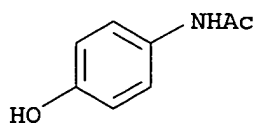


● HCl

CM 2

CRN 103-90-2

CMF C8 H9 N O2



2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 124:75606

REFERENCE 2: 118:261016

L85 ANSWER 16 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN

RN 147630-09-9 REGISTRY

ED Entered STN: 19 May 1993

CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with rel-(1R,2R)-2-
[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol (9CI) (CA INDEX
NAME)

OTHER CA INDEX NAMES:

CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with cis-(±)-2-
[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-,
(1R,2R)-rel-, mixt. contg. (9CI)

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, cis-(±)-,
mixt. contg.

OTHER NAMES:

CN Acetaminophen-tramadol mixt.

CN Ultracet

FS STEREOSEARCH

MF C16 H25 N O2 . C8 H9 N O2

CI MXS

SR CA

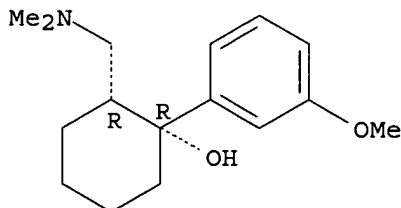
LC STN Files: CA, CAPLUS, DIOGENES, TOXCENTER

CM 1

CRN 27203-92-5

CMF C16 H25 N O2

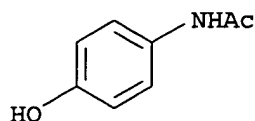
Relative stereochemistry.



CM 2

CRN 103-90-2

CMF C8 H9 N O2



13 REFERENCES IN FILE CA (1907 TO DATE)
14 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:254309
REFERENCE 2: 142:559
REFERENCE 3: 141:325105
REFERENCE 4: 141:128644
REFERENCE 5: 140:174755
REFERENCE 6: 139:317290
REFERENCE 7: 139:316390
REFERENCE 8: 139:206925
REFERENCE 9: 139:111543
REFERENCE 10: 137:195456

L85 ANSWER 17 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN

RN 147441-56-3 REGISTRY

ED Entered STN: 07 May 1993

CN Cyclohexanol, 2-[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)-,
(1R,2R)-rel- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, N-oxide,
cis-(±)-

OTHER NAMES:

CN Cyclohexanol, 2-[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)-, cis-

CN RWJ 38705

CN Tramadol N-oxide

FS STEREOSEARCH

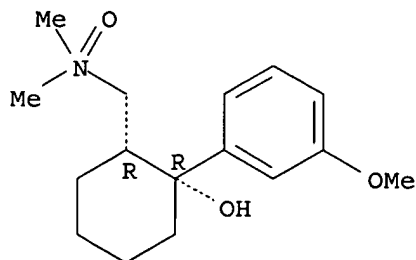
MF C16 H25 N O3

CI COM

SR CA

LC STN Files: ADISINSIGHT, BIOSIS, CA, CAPLUS, IPA, TOXCENTER, USPATFULL

Relative stereochemistry.



12 REFERENCES IN FILE CA (1907 TO DATE)
12 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:16861
REFERENCE 2: 140:228326
REFERENCE 3: 138:297047
REFERENCE 4: 138:66133
REFERENCE 5: 136:63545
REFERENCE 6: 134:202706
REFERENCE 7: 133:26418
REFERENCE 8: 125:265758
REFERENCE 9: 121:212995
REFERENCE 10: 120:261350

L85 ANSWER 18 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN

RN 144830-15-9 REGISTRY

ED Entered STN: 10 Dec 1992

CN Phenol, 3-[(1S,2S)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]- (9CI)
(CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Phenol, 3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, (1S-cis)-

OTHER NAMES:

CN (-)-O-Demethyltramadol

CN (-)-O-Desmethyltramadol

FS STEREOSEARCH

MF C15 H23 N O2

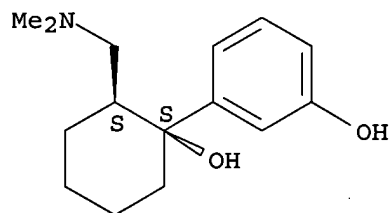
CI COM

SR CA

LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, CHEMCATS, CSCHEM, TOXCENTER,
USPAT2, USPATFULL

(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

24 REFERENCES IN FILE CA (1907 TO DATE)

24 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 141:150445
REFERENCE 2: 140:399213
REFERENCE 3: 140:263685

REFERENCE 4: 139:143236
REFERENCE 5: 139:46340
REFERENCE 6: 139:36331
REFERENCE 7: 138:82891
REFERENCE 8: 136:318793
REFERENCE 9: 135:146704
REFERENCE 10: 134:348298

L85 ANSWER 19 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN

RN 144830-14-8 REGISTRY

ED Entered STN: 10 Dec 1992

CN Phenol, 3-[(1R,2R)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]- (9CI)
(CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Phenol, 3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, (1R-cis)-

OTHER NAMES:

CN (+)-O-Demethyltramadol

CN (+)-O-Desmethyltramadol

FS STEREOSEARCH

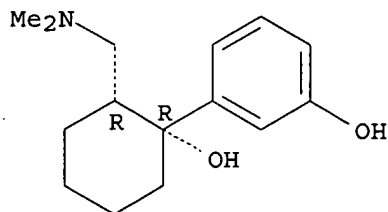
MF C15 H23 N O2

CI COM

SR CA

LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

29 REFERENCES IN FILE CA (1907 TO DATE)

1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

29 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 141:150445
REFERENCE 2: 140:399213
REFERENCE 3: 140:263685
REFERENCE 4: 139:159829
REFERENCE 5: 139:143236
REFERENCE 6: 139:46340
REFERENCE 7: 139:36331

REFERENCE 8: 138:248554

REFERENCE 9: 138:82891

REFERENCE 10: 137:206539

L85 ANSWER 20 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN

RN 80456-81-1 REGISTRY

ED Entered STN: 16 Nov 1984

CN Phenol, 3-[(1R,2R)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, rel-(9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Phenol, 3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, cis-(±)-

OTHER NAMES:

CN (RR,SS)-3-[2-[(Dimethylamino)methyl]-1-hydroxycyclohexyl]phenol

CN Mono-O-demethyltramadol

CN O-Demethyltramadol

CN O-Desmethyl tramadol

CN Phenol, 3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, cis-

FS STEREOSEARCH

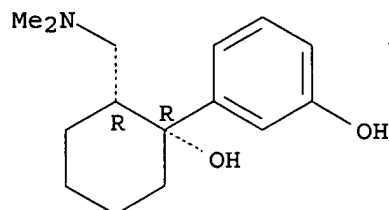
DR 138853-72-2, 147859-77-6, 185502-38-9

MF C15 H23 N O2

CI COM

LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, CHEMCATS, IPA, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

64 REFERENCES IN FILE CA (1907 TO DATE)

1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

64 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:68465

REFERENCE 2: 142:32417

REFERENCE 3: 141:401084

REFERENCE 4: 141:337401

REFERENCE 5: 141:270940

REFERENCE 6: 141:230849

REFERENCE 7: 140:363057

REFERENCE 8: 140:228837

REFERENCE 9: 140:228326

REFERENCE 10: 140:209862

L85 ANSWER 21 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN

RN 36282-47-0 REGISTRY

ED Entered STN: 16 Nov 1984

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-,
hydrochloride, (1R,2R)-rel- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-,
hydrochloride, cis-(±)-

OTHER NAMES:

CN (±)-trans-2-[(Dimethylamino)methyl]-1-(m-methoxyphenyl)cyclohexanol
hydrochloride

CN Adamon

CN Bellatram

CN CG 315

CN cis-Tramadol hydrochloride

CN Contramal

CN Crispin

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-,
hydrochloride, cis-

CN Dolana

CN Mabron

CN Melanate

CN NIH 10969

CN Omnidol

CN Radol

CN Tadol

CN Topalgic

CN Trabar

CN Tradol

CN Tradol-Puren

CN Tradonal

CN Tramadex

CN Tramadol hydrochloride

CN Tramagetic

CN Tramagit

CN Tramal

CN Tramazac

CN Tramed

CN Tramol

CN Tridol

CN Ultram

CN Zumatran

CN Zydol

FS STEREOSEARCH

DR 53611-16-8, 22204-88-2, 194602-08-9

MF C16 H25 N O2 . Cl H

CI COM

LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*,
BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS,
CHEMLIST, CIN, CSCHEM, DIOGENES, EMBASE, HSDB*, IMSCOSEARCH, IPA,
MEDLINE, MRCK*, PATDPASPC, PHAR, PROMT, PS, RTECS*, SYNTHLINE,
TOXCENTER, USAN, USPAT2, USPATFULL

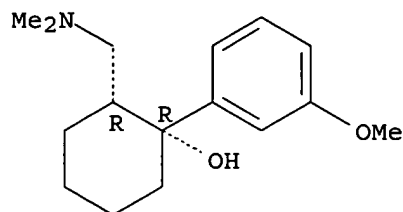
(*File contains numerically searchable property data)

Other Sources: EINECS**

(**Enter CHEMLIST File for up-to-date regulatory information)

CRN (27203-92-5)

Relative stereochemistry.



● HCl

257 REFERENCES IN FILE CA (1907 TO DATE)
 3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 259 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:246182
 REFERENCE 2: 142:190907
 REFERENCE 3: 142:168857
 REFERENCE 4: 142:127290
 REFERENCE 5: 142:127217
 REFERENCE 6: 142:126508
 REFERENCE 7: 142:74343
 REFERENCE 8: 142:48965
 REFERENCE 9: 142:43799
 REFERENCE 10: 142:43549

L85 ANSWER 22 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN

RN 35719-43-8 REGISTRY

ED Entered STN: 16 Nov 1984

CN Acetamide, N-(4-hydroxyphenyl)-, monopotassium salt (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Acetanilide, 4'-hydroxy-, monopotassium salt (8CI)

OTHER NAMES:

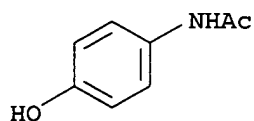
CN Potassium 4-(acetylamino)phenolate

CN Potassium 4-acetamidophenolate

MF C8 H9 N O2 . K

LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXCENTER, USPATFULL
 (*File contains numerically searchable property data)

CRN (103-90-2)



● K

13 REFERENCES IN FILE CA (1907 TO DATE)
13 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:321237

REFERENCE 2: 137:353010

REFERENCE 3: 135:14351

REFERENCE 4: 134:33001

REFERENCE 5: 132:54898

REFERENCE 6: 129:113538

REFERENCE 7: 125:142293

REFERENCE 8: 116:127907

REFERENCE 9: 105:42720

REFERENCE 10: 105:162

L85 ANSWER 23 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN

RN 27203-92-5 REGISTRY

ED Entered STN: 16 Nov 1984

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel-
(9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, cis-(±)-

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(m-methoxyphenyl)- (8CI)

OTHER NAMES:

CN (±)-Tramadol

CN CG 315E

CN cis-Tramadol

CN E 265

CN Racemic tramadol

CN Tramadol

CN U 26255A

FS STEREOSEARCH

DR 113683-92-4, 73806-46-9

MF C16 H25 N O2

CI COM

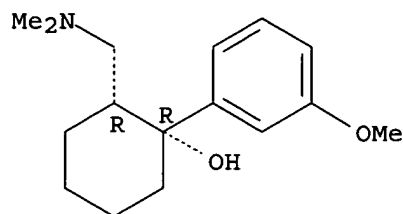
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*,
BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB,
CEN, CHEMCATS, CHEMLIST, CIN, DDFU, DIOGENES, DRUGU, EMBASE, HSDB*,
IMSCOSEARCH, IMSPATENTS, IPA, MEDLINE, MRCK*, PHAR, PROMT, PS, RTECS*,
SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU

(*File contains numerically searchable property data)

Other Sources: EINECS**, WHO

(**Enter CHEMLIST File for up-to-date regulatory information)

Relative stereochemistry.



****PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT****

855 REFERENCES IN FILE CA (1907 TO DATE)
 28 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 860 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:273874
 REFERENCE 2: 142:273362
 REFERENCE 3: 142:273292
 REFERENCE 4: 142:266935
 REFERENCE 5: 142:266843
 REFERENCE 6: 142:255934
 REFERENCE 7: 142:255929
 REFERENCE 8: 142:253394
 REFERENCE 9: 142:246187
 REFERENCE 10: 142:246171

L85 ANSWER 24 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN

RN 16958-94-4 REGISTRY

ED Entered STN: 16 Nov 1984

CN Acetamide, N-(4-hydroxyphenyl)-, monosodium salt (9CI) (CA INDEX NAME)

OTHER NAMES:

CN 4'-Hydroxyacetanilide sodium salt

CN 4-Hydroxyacetanilide sodium salt

CN N-Acetyl-p-aminophenol sodium

CN Sodium 4-(acetylamino)phenolate

CN Sodium 4-acetamidophenoxide

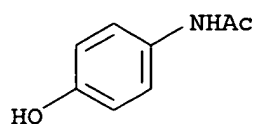
CN Sodium p-acetamidophenolate

MF C8 H9 N O2 . Na

LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, CHEMCATS, IFICDB, IFIPAT,
 IFIUDB, TOXCENTER, USPATFULL

(*File contains numerically searchable property data)

CRN (103-90-2)



● Na

29 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
29 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 136:167774
REFERENCE 2: 135:14351
REFERENCE 3: 134:178922
REFERENCE 4: 134:33001
REFERENCE 5: 132:189291
REFERENCE 6: 132:54898
REFERENCE 7: 129:244813
REFERENCE 8: 129:113538
REFERENCE 9: 128:145369
REFERENCE 10: 125:142293

L85 ANSWER 25 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN 103-90-2 REGISTRY
ED Entered STN: 16 Nov 1984
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Acetanilide, 4'-hydroxy- (7CI, 8CI)
OTHER NAMES:
CN 4'-Hydroxyacetanilide
CN 4-(Acetylamino)phenol
CN 4-(N-Acetylamino)phenol
CN 4-Acetamidophenol
CN 4-Acetaminophenol
CN 4-Hydroxyacetanilide
CN Abensanil
CN Acamol
CN Acenol
CN Acenol (pharmaceutical)
CN Acetagesic
CN Acetalgin
CN Acetaminofen
CN Acetaminophen
CN Algotropyl
CN Alpiny
CN Alvedon
CN Amadil
CN Anaflon
CN Anelix

CN Anhiba
CN Apamid
CN Apamide
CN APAP
CN Banesin
CN Ben-u-ron
CN Bickie-mol
CN Biocetamol
CN Calpol
CN Captin
CN Cetadol
CN Citramon P
CN Claratal
CN Clixodyne
CN Crocin
CN Dafalgan
CN Daphalgan
CN Datril
CN Dial-a-gesic
CN Dirox
CN Disprol
CN Doliprane
CN Dolprone
CN Duorol
CN Dymadon
CN Efferalgan
CN Endophy
CN Enelfa
CN Eneril

ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for
DISPLAY

FS 3D CONCORD

DR 8055-08-1

MF C8 H9 N O2

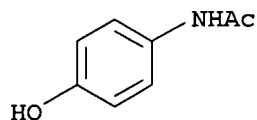
CI COM

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS,
BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB,
CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHM, CSNB, DDFU,
DETERM*, DIOGENES, DIPPR*, DRUGU, EMBASE, HODOC*, HSDB*, IFICDB,
IFIPAT, IFIUDB, IMSCOSEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC,
PATDPASPC, PHAR, PIRA, PROMT, PROUSDDR, PS, RTECS*, SPECINFO, SYNTHLINE,
TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL, VETU

(*File contains numerically searchable property data)

Other Sources: DSL**, EINECS**, TSCA**, WHO

(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

11399 REFERENCES IN FILE CA (1907 TO DATE)

257 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

11421 REFERENCES IN FILE CAPLUS (1907 TO DATE)

2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

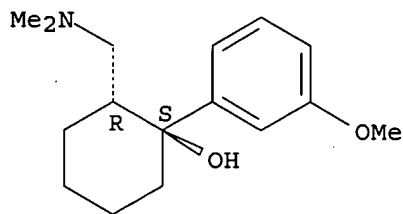
REFERENCE 1: 142:285039

REFERENCE 2: 142:284995
 REFERENCE 3: 142:284957
 REFERENCE 4: 142:280793
 REFERENCE 5: 142:279932
 REFERENCE 6: 142:275180
 REFERENCE 7: 142:274025
 REFERENCE 8: 142:273807
 REFERENCE 9: 142:266797
 REFERENCE 10: 142:266532

=> => d ide can tot

L86 ANSWER 1 OF 6 REGISTRY COPYRIGHT 2005 ACS on STN
 RN 181289-59-8 REGISTRY
 ED Entered STN: 26 Sep 1996
 CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1S,2R)-
 (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, trans-(-)-
 FS STEREOSEARCH
 MF C16 H25 N O2
 CI COM
 SR CA
 LC STN Files: CA, CAPLUS, CHEMCATS, CSCHEM, USPAT2, USPATFULL

Absolute stereochemistry. Rotation (-).



*F4I only-
used in search
strategy*

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

7 REFERENCES IN FILE CA (1907 TO DATE)
 7 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:263685
 REFERENCE 2: 139:36331
 REFERENCE 3: 137:288205
 REFERENCE 4: 136:79238
 REFERENCE 5: 134:348187
 REFERENCE 6: 132:298654

REFERENCE 7: 125:204663

L86 ANSWER 2 OF 6 REGISTRY COPYRIGHT 2005 ACS on STN

RN 181289-58-7 REGISTRY

ED Entered STN: 26 Sep 1996

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2S)-rel-(+)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, trans-(+)-

FS STEREOSEARCH

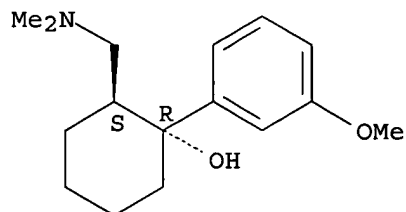
MF C16 H25 N O2

CI COM

SR CA

LC STN Files: CA, CAPLUS, CHEMCATS, CSChem, USPAT2, USPATFULL

Rotation (+). Absolute stereochemistry unknown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

7 REFERENCES IN FILE CA (1907 TO DATE)

7 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:74019

REFERENCE 2: 139:36331

REFERENCE 3: 137:288205

REFERENCE 4: 136:79238

REFERENCE 5: 134:348187

REFERENCE 6: 132:298654

REFERENCE 7: 125:204663

L86 ANSWER 3 OF 6 REGISTRY COPYRIGHT 2005 ACS on STN

RN 152538-36-8 REGISTRY

ED Entered STN: 27 Jan 1994

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2S)-rel-(9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, trans-

OTHER NAMES:

CN (+)-trans-Tramadol

CN trans-Tramadol

FS STEREOSEARCH

MF C16 H25 N O2

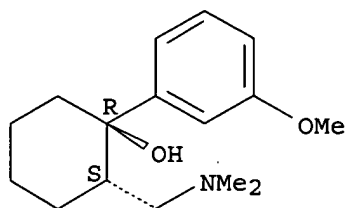
CI COM

SR CA

LC STN Files: ANABSTR, BIOSIS, CA, CAPLUS, CASREACT, TOXCENTER, USPAT2,

USPATFULL

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

26 REFERENCES IN FILE CA (1907 TO DATE)
 26 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:253603
 REFERENCE 2: 141:355563
 REFERENCE 3: 141:277348
 REFERENCE 4: 139:276697
 REFERENCE 5: 139:46340
 REFERENCE 6: 139:36331
 REFERENCE 7: 138:82891
 REFERENCE 8: 137:310691
 REFERENCE 9: 137:288205
 REFERENCE 10: 137:72521

L86 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2005 ACS on STN

RN 123154-38-1 REGISTRY

ED Entered STN: 13 Oct 1989

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-
 (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R-cis)-

OTHER NAMES:

CN (+)-(R,R)-trans-Tramadol

CN (+)-trans-Tramadol free base

FS STEREOSEARCH

DR 46941-74-6

MF C16 H25 N O2

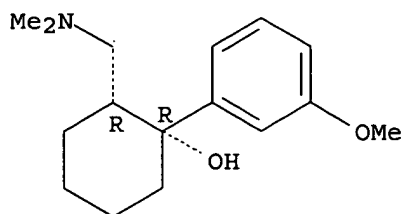
CI COM

SR CA

LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, RTECS*, TOXCENTER, USPAT2,
 USPATFULL

(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (+).



****PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT****

27 REFERENCES IN FILE CA (1907 TO DATE)
27 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 141:150445
REFERENCE 2: 140:263685
REFERENCE 3: 139:369878
REFERENCE 4: 139:46340
REFERENCE 5: 139:36331
REFERENCE 6: 138:248554
REFERENCE 7: 137:288205
REFERENCE 8: 137:72521
REFERENCE 9: 136:318793
REFERENCE 10: 136:177417

L86 ANSWER 5 OF 6 REGISTRY COPYRIGHT 2005 ACS on STN

RN 123134-25-8 REGISTRY

ED Entered STN: 13 Oct 1989

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1S,2S)-
(9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1S-cis)-

OTHER NAMES:

CN (-)-(S,S)-trans-Tramadol

FS STEREOSEARCH

DR 46941-76-8

MF C16 H25 N O2

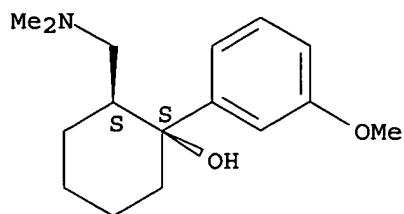
CI COM

SR CA

LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, RTECS*, TOXCENTER, USPAT2,
USPATFULL

(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

24 REFERENCES IN FILE CA (1907 TO DATE)
24 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 141:150445
REFERENCE 2: 139:369878
REFERENCE 3: 139:46340
REFERENCE 4: 139:36331
REFERENCE 5: 137:288205
REFERENCE 6: 137:226635
REFERENCE 7: 137:72521
REFERENCE 8: 136:318793
REFERENCE 9: 136:177417
REFERENCE 10: 135:357725

L86 ANSWER 6 OF 6 REGISTRY COPYRIGHT 2005 ACS on STN

RN 2914-77-4 REGISTRY

ED Entered STN: 16 Nov 1984

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(m-methoxyphenyl)- (7CI)

OTHER NAMES:

CN 1-(m-Methoxyphenyl)-2-[(dimethylamino)methyl]cyclohexanol

CN 2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol

FS 3D CONCORD

MF C16 H25 N O2

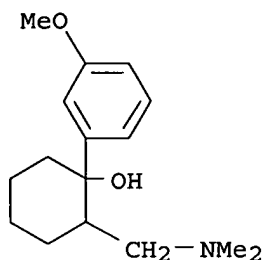
CI COM

LC STN Files: BEILSTEIN*, BIOSIS, CA, CAOLD, CAPLUS, CHEMCATS, CHEMLIST, RTECS*, TOXCENTER, USPAT2, USPATFULL

(*File contains numerically searchable property data)

Other Sources: EINECS**

(**Enter CHEMLIST File for up-to-date regulatory information)



****PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT****

10 REFERENCES IN FILE CA (1907 TO DATE)
10 REFERENCES IN FILE CAPLUS (1907 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 142:16861
REFERENCE 2: 139:276697
REFERENCE 3: 139:202672
REFERENCE 4: 134:56474
REFERENCE 5: 126:293443
REFERENCE 6: 82:21817
REFERENCE 7: 80:128176
REFERENCE 8: 80:128175
REFERENCE 9: 76:153321
REFERENCE 10: 63:54418

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 08:00:31 ON 06 APR 2005

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FILE COVERS 1907 - 6 Apr 2005 VOL 142 ISS 15

FILE LAST UPDATED: 5 Apr 2005 (20050405/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all hitstr tot 184

L84 ANSWER 1 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2002:256052 HCAPLUS

DN 136:284456

ED Entered STN: 05 Apr 2002

TI Analgesic and glucosamine compositions

IN **Raffa, Robert**; Cowan, Alan; Tallarida, Ronald

PA Temple University, USA

SO PCT Int. Appl., 24 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-70

CC 63-6 (Pharmaceuticals)

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002026239	A1	20020404	WO 2001-US29606	20010921
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	CA 2423585	AA	20020404	CA 2001-2423585	20010921
	AU 2001092929	A5	20020408	AU 2001-92929	20010921
	EP 1328278	A1	20030723	EP 2001-973339	20010921
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
	US 2002058642	A1	20020516	US 2001-964178	20010925
PRAI	US 2000-235405P	P	20000926		
	WO 2001-US29606	W	20010921		

CLASS

	PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
	WO 2002026239	ICM	A61K031-70
	US 2002058642	ECLA	A61K031/00+A; A61K031/192; A61K031/70B+M
AB	This invention relates to a composition a glucosamine material and an analgesic compound such as a nonsteroidal anti-inflammatory drug (NSAID) and/or an opioid analgesic and its use for treatment of pain in pharmaceutical or veterinary applications. When the components are administered within certain ratios, the analgesic efficacy of the composition is super-additive (synergistic) relative to the analgesic efficacy of the analgesic compound alone. Solns. of glucosamine with ibuprofen or ketoprofen were given.		
ST	analgesic NSAID glucosamine compn		
IT	Analgesics		
	Antiarthritics		
	Antihistamines		
	Bronchodilators		
	Decongestants		
	Muscle relaxants		
	(analgesic and glucosamine compns.)		
IT	Anti-inflammatory agents		
	(nonsteroidal; analgesic and glucosamine compns.)		
IT	Drug interactions		
	(synergistic; analgesic and glucosamine compns.)		
IT	66-84-2, Glucosamine hydrochloride 103-90-2, Acetaminophen 3416-24-8, Glucosamine 7512-17-6,		

N-Acetylglucosamine 15307-86-5, Diclofenac 15687-27-1, Ibuprofen
22071-15-4, Ketoprofen 27203-92-5, Tramadol
29031-19-4, Glucosamine sulfate

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(analgesic and glucosamine compns.)

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

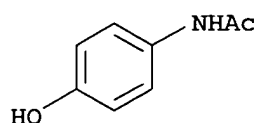
(1) Armitage; US 4501727 A 1985 HCAPLUS

IT 103-90-2, Acetaminophen 27203-92-5,
Tramadol

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(analgesic and glucosamine compns.)

RN 103-90-2 HCAPLUS

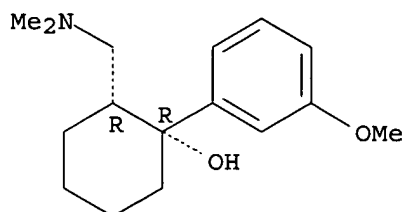
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



RN 27203-92-5 HCAPLUS

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel-
(9CI) (CA INDEX NAME)

Relative stereochemistry.



L84 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2001:833143 HCAPLUS

DN 135:362611

ED Entered STN: 16 Nov 2001

TI Opioid antagonist compositions and dosage forms

IN Sherman, Barry; Remien, Mary; Barbier, Remi; McGinity, James W.

PA Pain Therapeutics, Inc., USA; Albert Einstein College of Medicine of
Yeshiva University

SO PCT Int. Appl., 116 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61P

CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 1

FAN.CNT 13

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001085257	A2	20011115	WO 2001-US14377	20010504
	WO 2001085257	A3	20020613		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,				

RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
 VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
 BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6011004 A 20000104 US 1996-768221 19961217 <--
 AU 9947399 A1 19991028 AU 1999-47399 19990906
 WO 2000067739 A2 20001116 WO 2000-US12493 20000505
 WO 2000067739 A3 20010125

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR,
 CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
 ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
 LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,
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 CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2408106 AA 20011115 CA 2001-2408106 20010504
 AU 2001059458 A5 20011120 AU 2001-59458 20010504
 EP 1284736 A2 20030226 EP 2001-932983 20010504

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

JP 2004515455 T2 20040527 JP 2001-581910 20010504

PRAI US 2000-20227P P 20000505
 US 2000-202268P P 20000505
 US 2000-566071 A 20000505
 WO 2000-US12493 W 20000505
 US 2000-244482P P 20001030
 US 2000-245110P P 20001101
 US 2000-246235P P 20001102
 US 2001-756331 A 20010108
 US 1990-612847 B1 19901113 <--
 US 1993-153796 A1 19931117
 AU 1995-32769 A3 19950718
 US 1999-306164 A2 19990506
 WO 2001-US14377 W 20010504

CLASS

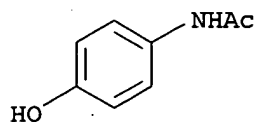
PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2001085257	ICM	A61P
US 6011004	ECLA	A61K038/18F+M
JP 2004515455	FTERM	4C076/AA36; 4C076/AA44; 4C076/AA53; 4C076/BB01; 4C076/CC01; 4C076/CC04; 4C076/EE42H; 4C076/FF33; 4C084/AA17; 4C084/AA20; 4C084/AA23; 4C084/AA24; 4C084/MA02; 4C084/MA05; 4C084/MA35; 4C084/MA37; 4C084/MA52; 4C084/NA05; 4C084/NA11; 4C084/ZA082; 4C086/AA01; 4C086/AA02; 4C086/BC21; 4C086/CB23; 4C086/DA08; 4C086/MA01; 4C086/MA02; 4C086/NA05; 4C086/NA11; 4C086/ZA02; 4C086/ZA05; 4C086/ZA08; 4C086/ZB11; 4C206/AA01; 4C206/AA02; 4C206/FA10; 4C206/GA02; 4C206/GA31; 4C206/MA01; 4C206/MA02; 4C206/MA03; 4C206/MA04; 4C206/MA05; 4C206/MA55; 4C206/MA57; 4C206/MA72; 4C206/NA05; 4C206/NA06; 4C206/NA11; 4C206/ZA02; 4C206/ZA05; 4C206/ZA08; 4C206/ZB11

AB The present invention is directed to novel dosage forms, pharmaceutical compns., kits, and methods of administration of an opioid antagonist at 0.0001-1.0 mg, including 0.0001-0.5 mg. Solid oral dosage forms are disclosed consisting essentially of an opioid antagonist or alternatively comprising an opioid antagonist and another active ingredient, such as an opioid agonist. Immediate release oral dosage forms are disclosed that release all or a substantial percentage of opioid antagonist, and another

active ingredient when present, in a desired time. Concurrent release dosage forms are disclosed that provide concurrent release of an opioid antagonist and another active ingredient. Thus, a suspension contained morphine sulfate (opioid agonist) 20, naltrexone (opioid antagonist) 0.05, talc 10, and Miglyol-812 qs to 100%.

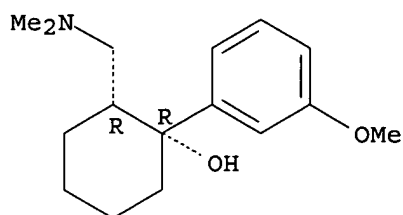
- ST opioid antagonist agonist pharmaceutical; morphine naltrexone pharmaceutical
- IT Glycerides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C8-10; opioid antagonist dosage forms)
- IT Drug delivery systems
(beads; opioid antagonist dosage forms)
- IT Drug delivery systems
(capsules; opioid antagonist dosage forms)
- IT Drug delivery systems
(granules; opioid antagonist dosage forms)
- IT Drug delivery systems
(immediate-release; opioid antagonist dosage forms)
- IT Anti-inflammatory agents
(nonsteroidal; opioid antagonist dosage forms)
- IT Analgesics
Anti-inflammatory agents
Containers
Dissolution rate
Opioid antagonists
Plasticizers
(opioid antagonist dosage forms)
- IT Opioids
Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(opioid antagonist dosage forms)
- IT Drug delivery systems
(pellets; opioid antagonist dosage forms)
- IT Drug delivery systems
(solids, oral; opioid antagonist dosage forms)
- IT Drug delivery systems
(tablets; opioid antagonist dosage forms)
- IT 329900-75-6, COX 2 329967-85-3, COX-1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; opioid antagonist dosage forms)
- IT 9004-34-6, Cellulose, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(microcryst.; opioid antagonist dosage forms)
- IT 57-27-2, Morphine, biological studies 57-42-1, Meperidine 57-50-1, Sucrose, biological studies 63-42-3, Lactose 64-31-3, Morphine sulfate 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-99-3, Methadone 103-90-2, **Acetaminophen** 124-90-3, Oxycodone hydrochloride 125-29-1, Hydrocodone 143-71-5, Hydrocodone bitartrate 437-38-7, Fentanyl 465-65-6, Naloxone 466-99-9, Hydromorphone 469-62-5, Propoxyphene 557-04-0 7757-93-9, Dibasic calcium phosphate 7789-77-7, Emcompress 9004-64-2, Hydroxypropyl cellulose 9004-65-3, HPMC 14807-96-6, Talc, biological studies 16590-41-3, Naltrexone 16676-29-2, Naltrexone hydrochloride 25322-68-3, Polyethylene glycol 27203-92-5, **Tramadol** 36282-47-0, **Tramadol hydrochloride** 55096-26-9, Nalmefene 71195-58-9, Alfentanil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(opioid antagonist dosage forms)
- IT 103-90-2, **Acetaminophen** 27203-92-5, **Tramadol** 36282-47-0, **Tramadol hydrochloride**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(opioid antagonist dosage forms)

RN 103-90-2 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



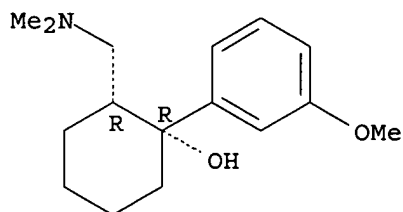
RN 27203-92-5 HCAPLUS
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 36282-47-0 HCAPLUS
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● HCl

L84 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:833071 HCAPLUS
DN 135:352822
ED Entered STN: 16 Nov 2001
TI Opioid agonist and antagonist compositions and methods for enhancing potency or reducing adverse side effects of opioid agonists
IN Sherman, Barry; Remien, Mary; Barbier, Remi; Dumas, Kathleen; Schoenhard, Grant
PA Pain Therapeutics, Inc., USA; Albert Einstein College of Medicine of Yeshiva University
SO PCT Int. Appl., 835 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-00
CC 1-11 (Pharmacology)

Section cross-reference(s): 63

FAN.CNT 13

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001085150	A2	20011115	WO 2001-US14644	20010504
	WO 2001085150	A3	20020808		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
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	WO 2000067739	A2	20001116	WO 2000-US12493	20000505
	WO 2000067739	A3	20010125		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	CA 2408098	AA	20011115	CA 2001-2408098	20010504
	EP 1280529	A2	20030205	EP 2001-933110	20010504
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
	JP 2004501094	T2	20040115	JP 2001-581804	20010504
PRAI	US 2000-202227P	P	20000505		
	US 2000-202268P	P	20000505		
	US 2000-566071	A	20000505		
	WO 2000-US12493	W	20000505		
	US 2000-244482P	P	20001030		
	US 2000-245110P	P	20001101		
	US 2000-246235P	P	20001102		
	US 2001-756331	A	20010108		
	US 1990-612847	B1	19901113	<--	
	US 1993-153796	A1	19931117		
	AU 1995-32769	A3	19950718		
	US 1999-306164	A2	19990506		
	WO 2001-US14644	W	20010504		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2001085150	ICM	A61K031-00
US 6011004	ECLA	A61K038/18F+M
JP 2004501094	FTERM	4C086/AA01; 4C086/AA02; 4C086/CB23; 4C086/MA02; 4C086/MA04; 4C086/MA05; 4C086/MA52; 4C086/MA56; 4C086/MA63; 4C086/MA66; 4C086/NA05; 4C086/NA06; 4C086/ZA08; 4C086/ZC02; 4C086/ZC75; 4C206/AA01; 4C206/AA02; 4C206/GA02; 4C206/GA31; 4C206/KA01; 4C206/MA02; 4C206/MA04; 4C206/MA05; 4C206/MA72; 4C206/MA76; 4C206/MA83; 4C206/MA86; 4C206/NA05; 4C206/NA06; 4C206/ZA08; 4C206/ZC02; 4C206/ZC75

AB The invention provides compns. and methods using an opioid agonist and an opioid antagonist to differentially dose a human subject so as to either enhance analgesic potency without attenuating an adverse side effect of the agonist, or alternatively maintain the analgesic potency of the

agonist while attenuating an adverse side effect of the agonist. The invention addnl. relates to novel opioid compns. and methods for the gender-based dosing of men and women.

ST adverse effect opioid agonist antagonist dosing; gender dosing opioid agonist antagonist; opioid agonist antagonist dosing analgesia

IT Puerperium
(and perinatal conditions; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Disease, animal
(asthenia; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Inflammation
(cellulitis; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Eye, disease
(conjunctivitis; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Intestine, disease
(constipation; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Biliary tract
Cardiovascular system
Connective tissue
Digestive tract
Ear
Joint, anatomical
Mammary gland
Nervous system
Prostate gland
Skeleton
Urinary tract
(disease; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Sleep
Vision
(disorder; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Toxicity
(drug; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Breathing (animal)
(dyspnea; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Urinary tract
(dysuria; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Nose
(epistaxis; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Emotion
(euphoria; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Skin
(flush; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Mental disorder
(hallucinations; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Urine
(hematuria; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Reflex

(hiccup; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Muscle, disease
(hypertonia; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Tooth
(infection; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Drug delivery systems
(injections, i.m.; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Drug delivery systems
(injections, i.v.; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Drug delivery systems
(injections, s.c.; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Taste
(loss; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Headache
(migraine; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Drug delivery systems
(mucosal; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Muscle, disease
(myalgia; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Pharynx
(nasopharynx, nasopharyngitis; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Adenoma
Analgesics
Anxiety
Blood pressure
Blood vessel, disease
Body temperature
Bone, disease
Calculi, biliary
Cough
Dermatitis
Diarrhea
Dizziness
Drug delivery systems
Drug interactions
Dysmenorrhea
Dyspepsia
Erythema
Eye, disease
Fatigue, biological
Fever and Hyperthermia
Flatulence
Headache
Hearing
Heart rate
Hemorrhage
Hypertension
Hypotension

Hypothermia
 Infection
 Injury
 Kidney, disease
 Mental disorder
 Miosis
 Muscle, disease
 Nausea
 Neoplasm
 Opioid antagonists
 Pain
 Poisoning, biological
 Pregnancy
 Pruritus
 Reproductive tract
 Respiratory tract
 Sex
 Skin, disease
 Sweat
 Testis, disease
 Tremor
 Urogenital tract
 Urticaria
 Vasodilation
 Vomiting

(opioid agonist and antagonist compns. and methods for enhancing
 potency or reducing adverse side effects of opioid agonists)

IT Opioids

RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
 (Uses)

(opioid agonist and antagonist compns. and methods for enhancing
 potency or reducing adverse side effects of opioid agonists)

IT Mouth

(oral pain; opioid agonist and antagonist compns. and methods for
 enhancing potency or reducing adverse side effects of opioid agonists)

IT Drug delivery systems

(oral; opioid agonist and antagonist compns. and methods for enhancing
 potency or reducing adverse side effects of opioid agonists)

IT Abdomen

(pain; opioid agonist and antagonist compns. and methods for enhancing
 potency or reducing adverse side effects of opioid agonists)

IT Pharynx

(pharyngitis; opioid agonist and antagonist compns. and methods for
 enhancing potency or reducing adverse side effects of opioid agonists)

IT Skin, disease

(photosensitivity; opioid agonist and antagonist compns. and methods
 for enhancing potency or reducing adverse side effects of opioid
 agonists)

IT Skin, disease

(rash; opioid agonist and antagonist compns. and methods for enhancing
 potency or reducing adverse side effects of opioid agonists)

IT Nose

(rhinitis; opioid agonist and antagonist compns. and methods for
 enhancing potency or reducing adverse side effects of opioid agonists)

IT Mental activity

(sedation; opioid agonist and antagonist compns. and methods for
 enhancing potency or reducing adverse side effects of opioid agonists)

IT Organ, animal

(sensory; opioid agonist and antagonist compns. and methods for
 enhancing potency or reducing adverse side effects of opioid agonists)

IT Tremor

(shivering; opioid agonist and antagonist compns. and methods for

enhancing potency or reducing adverse side effects of opioid agonists)

IT Eyestalk
(sinus gland, congestion; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Muscle, disease
(spasm; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Mouth
(stomatitis; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Drug delivery systems
(sublingual; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Brain, disease
(syncope; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Heart, disease
(tachycardia; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Ear
(tinnitus; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Drug delivery systems
(transdermal; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Muscle
(twitch; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Respiratory tract
(upper, infection; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Urine
(urinary retention; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Mouth
(xerostomia; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Opioid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(μ -opioid; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT 57-27-2, Morphine, biological studies 64-31-3, Morphine sulfate
76-42-6, Oxycodone 125-29-1, Hydrocodone 27203-92-5,
Tramadol 36282-47-0, Tramadol
hydrochloride 330988-71-1, Hydrocet
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT 103-90-2, Acetaminophen 465-65-6, Naloxone
16590-41-3, Naltrexone 16676-29-2, Naltrexone hydrochloride
55096-26-9, Nalmefene
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT 27203-92-5, Tramadol 36282-47-0,

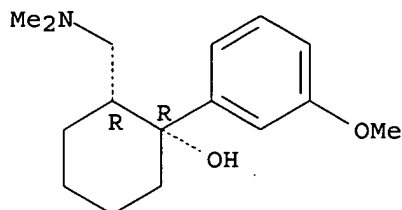
Tramadol hydrochloride

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

RN 27203-92-5 HCAPLUS

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

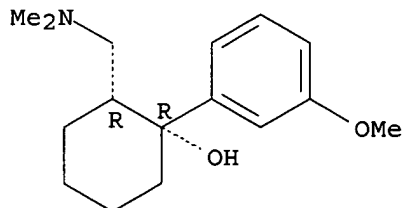
Relative stereochemistry.



RN 36282-47-0 HCAPLUS

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● HCl

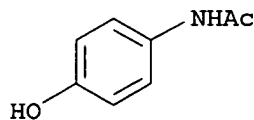
IT 103-90-2, Acetaminophen

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

RN 103-90-2 HCAPLUS

CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2001:732199 HCAPLUS

DN 136:31212

ED Entered STN: 08 Oct 2001

TI Pharmacology of oral combination analgesics: Rational therapy for pain
 AU **Raffa, R. B.**
 CS Temple University School of Pharmacy, Philadelphia, PA, 19140, USA
 SO Journal of Clinical Pharmacy and Therapeutics (2001), 26(4), 257-264
 CODEN: JCPTED; ISSN: 0269-4727
 PB Blackwell Science Ltd.
 DT Journal; General Review
 LA English
 CC 1-0 (Pharmacology)
 AB A review.s. No single analgesic agent is perfect and no single analgesic can treat all types of pain. Yet each agent has distinct advantages and disadvantages compared to the others. Hence, clin. outcomes might be improved under certain conditions with the use of a combination of analgesics, rather than reliance on a single agent. A combination is most effective when the individual agents act through different analgesic mechanisms and act synergistically. By activating multiple pain-inhibitory pathways, combination analgesics can provide more effective pain relief for a broader spectrum of pain, and might also reduce adverse drug reactions. This overview highlights the therapeutic potential of combining analgesic medications with different mechanisms of action, particularly a nonsteroidal anti-inflammatory drug (NSAID) or **acetaminophen** with an opioid or **tramadol**.
 ST review NSAID **acetaminophen** opioid **tramadol** analgesic combination pain
 IT Anti-inflammatory agents
 (nonsteroidal; pharmacol. of oral combination analgesics for pain in humans)
 IT Analgesics
 Human
 (pharmacol. of oral combination analgesics for pain in humans)
 IT Opioids
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (pharmacol. of oral combination analgesics for pain in humans)
 IT Drug interactions
 (synergistic; pharmacol. of oral combination analgesics for pain in humans)
 IT 103-90-2, **Acetaminophen** 27203-92-5, **Tramadol**
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (pharmacol. of oral combination analgesics for pain in humans)
 RE.CNT 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD
 RE
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IT 103-90-2, Acetaminophen 27203-92-5,

Tramadol

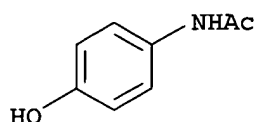
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)

(pharmacol. of oral combination analgesics for pain in humans)

RN 103-90-2 HCAPLUS

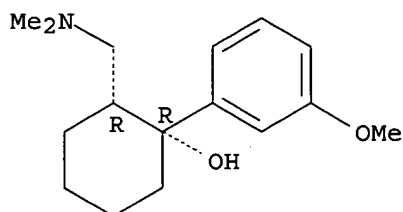
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



RN 27203-92-5 HCAPLUS

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L84 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2000:875749 HCAPLUS

DN 134:33001

ED Entered STN: 14 Dec 2000

TI Alkali metal and alkaline-earth metal salts of **acetaminophen**

IN Ohannesian, Lena A.; Nadig, David; Higgins, John D., III; Rey, Max; Martellucci, Stephen A.

PA McNeil-PPC, Inc., USA

SO U.S., 10 pp., Cont.-in-part of U.S. Ser. No. 987,210, abandoned.

CODEN: USXXAM

DT Patent

LA English

IC ICM A61K031-16

ICS C07C233-00

NCL 514629000

CC 63-6 (Pharmaceuticals)

FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI:	US 6160020	A	20001212	US 1998-100284	19980619
	WO 9966919	A1	19991229	WO 1999-US13064	19990609
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,				

ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
 CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9943380	A1	20000110	AU 1999-43380	19990609
PRAI US 1996-771176	B2	19961220		
US 1997-987210	B2	19971209		
US 1998-100284	A	19980619		
WO 1999-US13064	W	19990609		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 6160020	ICM	A61K031-16
	ICS	C07C233-00
	NCL	514629000
US 6160020	ECLA	A61K031/167; A61K045/06; C07C233/25
WO 9966919	ECLA	A61K031/167; A61K045/06
AB		Isolated salts of acetaminophen are disclosed. Alkali metal and alkaline-earth metal salts of acetaminophen are formed by reacting the free acid of acetaminophen with the corresponding metal hydroxide and then immediately isolating the resulting salt. These salts have been found to be more water soluble and less bitter in taste than the free acid form of acetaminophen . The isolated salts may also be combined with other active ingredients. A tablet contained calcium acetaminophen 368.23, chlorpheniramine maleate 2, microcryst. cellulose 520.77, silica 4.5, and Mg stearate 4.5 mg.
ST		acetaminophen metal salt prepn tablet; tablet calcium acetaminophen chlorpheniramine maleate
IT		Drugs (gastrointestinal; oral compns. containing acetaminophen metal salt and other actives)
IT		Analgesics Antihistamines Antipyretics Antitussives Bronchodilators Decongestants Diuretics Drug bioavailability Expectorants Hypnotics and Sedatives (oral compns. containing acetaminophen metal salt and other actives)
IT		Drug delivery systems (oral; oral compns. containing acetaminophen metal salt and other actives)
IT		Drug delivery systems (tablets; oral compns. containing acetaminophen metal salt and other actives)
IT		209967-47-5P RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (oral compns. containing acetaminophen metal salt and other actives)
IT		50-78-2, Acetyl salicylic acid 51-43-4, Epinephrine 51-55-8, Atropine, biological studies 53-86-1, Indomethacin 58-08-2, Caffeine, biological studies 58-55-9, Theophylline, biological studies 58-73-1, Diphenhydramine 59-33-6, Pyrilamine 59-42-7, Phenylephrine 60-87-7, Promethazine 68-88-2, Hydroxyzine 73-31-4, Melatonin 76-42-6, Oxycodone 76-57-3, Codeine 77-09-8, Phenolphthalein 77-19-0, Dicyclomine 77-22-5, Caramiphen 77-23-6, Carbetapentane 86-22-6, Brompheniramine 90-82-4, Pseudoephedrine 91-81-6, Tripeleminamine 93-14-1, Guaifenesin 104-31-4, Benzonatate; 113-92-8 125-29-1, Hydrocodone 125-71-3, Dextromethorphan 128-62-1, Noscapine 129-03-3,

Cyproheptadine 132-21-8, Dexbrompheniramine 299-42-3, Ephedrine; 317-34-0, Aminophylline 364-62-5, Metoclopramide 466-99-9, Hydromorphone 471-34-1, Calcium carbonate, biological studies 486-12-4, Triprolidine 554-10-9, 3-Iodo-1,2-propanediol 562-10-7, Doxylamine 586-06-1, Metaproterenol 606-04-2, Pamabrom. 616-91-1 642-72-8, Benzydamine 791-35-5, Chlophedianol 915-30-0, Diphenoxylate 2451-01-6, Terpin hydrate 3572-43-8, Bromhexine 3964-81-6, Azatadine 5104-49-4, Flurbiprofen 7020-55-5, Clidinium 7683-59-2, Isoprenaline 8050-81-5, Simethicone 12125-02-9, Ammonium chloride, biological studies 14838-15-4, Phenylpropanolamine 14882-18-9, Bismuth subsalicylate 15307-86-5, Diclofenac 15687-27-1, Ibuprofen **16958-94-4** 18053-31-1, Fominoben 18559-94-9, Albuterol; 18683-91-5, Ambroxol 21645-51-2, Aluminum hydroxide, biological studies 22071-15-4, Ketoprofen 22204-53-1, Naproxen 23031-25-6, Terbutaline 25523-97-1, Dexchlorpheniramine **27203-92-5**, Tramadol 29679-58-1, Fenoprofen 29975-16-4, Estazolam 30392-40-6, Bitolterol 33005-95-7, Tiaprofenic acid 34580-13-7, Ketotifen **35719-43-8** 36322-90-4, Piroxicam 36950-96-6, Cicloprofen 38194-50-2, Sulindac 41340-25-4, Etodolac 42924-53-8, Nabumetone 50679-08-8, Terfenadine 51481-61-9, Cimetidine 51803-78-2, Nimesulide 53179-11-6, Loperamide; 53716-49-7, Carprofen 54182-58-0, Sucralfate 57644-54-9, Bismuth subcitrate 61869-07-6, Domiodol 66357-35-5, Ranitidine 68844-77-9, Astemizole 71125-38-7, Meloxicam 73590-58-6, Omeprazole 74103-06-3, Ketorolac 74978-16-8, Magaldrate 75970-99-9, Norastemizole 76824-35-6, Famotidine 76963-41-2, Nizatidine 79794-75-5, Loratidine 80937-31-1, Flosulide 81098-60-4, Cisapride 82626-48-0, Zolpidem 83799-24-0, Fexofenadine; 83881-51-0, Cetirizine 86181-42-2, Temelastine 87848-99-5, Acrivastine 169590-42-5, Celecoxib 180200-68-4 **209967-48-6 209967-50-0 209967-51-1**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(oral compns. containing **acetaminophen** metal salt and other actives)

IT **209967-42-0P 209967-44-2P 209967-45-3P 209967-46-4P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of **acetaminophen** metal salt to improve water solubility and taste)

IT **103-90-2, Acetaminophen** 1305-62-0, Calcium hydroxide, reactions 1310-65-2, Lithium hydroxide 1310-73-2, Sodium hydroxide, reactions 10043-52-4, Calcium chloride, reactions

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of **acetaminophen** metal salt to improve water solubility and taste)

RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

- (1) Anon; 1975, P506 HCAPLUS
- (2) Anon; GB 1428803 1976 HCAPLUS
- (3) Anon; RU 629209 1976
- (4) Anon; 1978, 11, HCAPLUS
- (5) Anon; GB 1514225 1978
- (6) Anon; FR 2417494 1979 HCAPLUS
- (7) Anon; 1980 HCAPLUS
- (8) Anon; IN 172949 1994 HCAPLUS
- (9) Anon; 1994, P1354 HCAPLUS
- (10) Anon; 1996 HCAPLUS
- (11) Anon; RU 1803833 A1 1998
- (12) Anon; Merck Index, 10th ed 1983, P43
- (13) Brand; US 4681897 1987 HCAPLUS

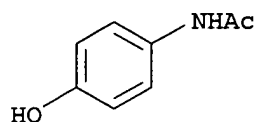
- (14) Brand; US 4812446 1989 HCAPLUS
- (15) Getz; J Org Chem 1992, V57(6), P1702 HCAPLUS
- (16) Harfenist; US 3862226 1975 HCAPLUS
- (17) Higuchi; US 3956490 1976 HCAPLUS
- (18) Kovach, I; Diss Abstr, Int B 1975, V36(2), P734
- (19) Mauskop; US 5538959 1996 HCAPLUS
- (20) Mauskop; US 5914129 1999 HCAPLUS
- (21) Robertson; US 3431293 1969 HCAPLUS
- (22) Rohrbach; US 3987170 1976
- (23) Simmons; US 5273759 1993 HCAPLUS
- (24) Stewart; US 2680097 1954 HCAPLUS
- (25) Sunshine; US 4552899 1985 HCAPLUS
- (26) Sunshine; US 4619934 1986 HCAPLUS
- (27) Sunshine; US 4783465 1988 HCAPLUS
- (28) Wilbert; US 2998450 1961 HCAPLUS
- (29) Young; US 2852540 1958 HCAPLUS
- (30) Yu; US 5360615 1994 HCAPLUS

IT 209967-47-5P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(oral compns. containing **acetaminophen** metal salt and other actives)

RN 209967-47-5 HCAPLUS

CN Acetamide, N-(4-hydroxyphenyl)-, calcium salt (2:1) (9CI) (CA INDEX NAME)



● 1/2 Ca

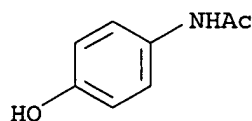
IT 16958-94-4 27203-92-5, Tramadol
35719-43-8 209967-48-6 209967-50-0
209967-51-1

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(oral compns. containing **acetaminophen** metal salt and other actives)

RN 16958-94-4 HCAPLUS

CN Acetamide, N-(4-hydroxyphenyl)-, monosodium salt (9CI) (CA INDEX NAME)



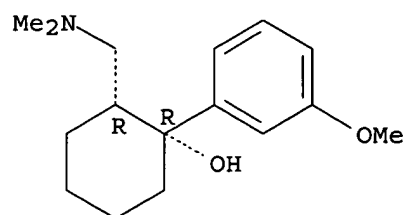
● Na

RN 27203-92-5 HCAPLUS

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel-

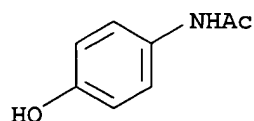
(9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 35719-43-8 HCAPLUS

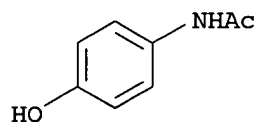
CN Acetamide, N-(4-hydroxyphenyl)-, monopotassium salt (9CI) (CA INDEX NAME)



● K

RN 209967-48-6 HCAPLUS

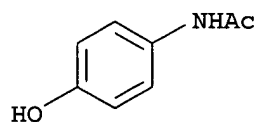
CN Acetamide, N-(4-hydroxyphenyl)-, monolithium salt (9CI) (CA INDEX NAME)



● Li

RN 209967-50-0 HCAPLUS

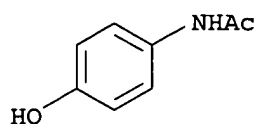
CN Acetamide, N-(4-hydroxyphenyl)-, monocationium salt (9CI) (CA INDEX NAME)



● Cs

RN 209967-51-1 HCAPLUS

CN Acetamide, N-(4-hydroxyphenyl)-, magnesium salt (2:1) (9CI) (CA INDEX NAME)



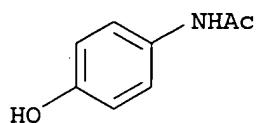
● 1/2 Mg

IT 209967-42-0P 209967-44-2P 209967-45-3P
209967-46-4P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of **acetaminophen** metal salt to improve water solubility and taste)

RN 209967-42-0 HCAPLUS

CN Acetamide, N-(4-hydroxyphenyl)-, monosodium salt, hexahydrate (9CI) (CA INDEX NAME)

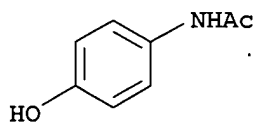


● Na

● 6 H₂O

RN 209967-44-2 HCAPLUS

CN Acetamide, N-(4-hydroxyphenyl)-, monosodium salt, heptahydrate (9CI) (CA INDEX NAME)



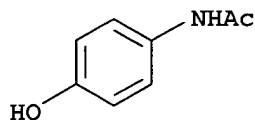
● Na

● 7 H₂O

RN 209967-45-3 HCAPLUS

CN Acetamide, N-(4-hydroxyphenyl)-, calcium salt (2:1), dihydrate (9CI) (CA

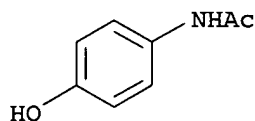
INDEX NAME)



● 1/2 Ca

● H₂O

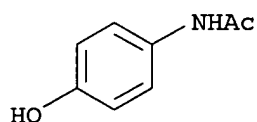
RN 209967-46-4 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)-, monolithium salt, hexahydrate (9CI) (CA INDEX NAME)



● Li

● 6 H₂O

IT 103-90-2, **Acetaminophen**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of **acetaminophen** metal salt to improve water solubility and taste)
RN 103-90-2 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:819235 HCAPLUS
DN 132:54898
ED Entered STN: 30 Dec 1999
TI Pharmaceutical composition containing a salt of **acetaminophen** and at least one other active ingredient
IN Ohannesian, Lena A.; Nadig, David; Higgins, John D., III; Rey, Max; Martellucci, Stephen A.

PA Mcneil-PPC, Inc., USA
 SO PCT Int. Appl., 31 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM A61K031-165
 CC 63-6 (Pharmaceuticals)
 FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9966919	A1	19991229	WO 1999-US13064	19990609
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 6160020	A	20001212	US 1998-100284	19980619
	AU 9943380	A1	20000110	AU 1999-43380	19990609
PRAI	US 1998-100284	A	19980619		
	US 1996-771176	B2	19961220		
	US 1997-987210	B2	19971209		
	WO 1999-US13064	W	19990609		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
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WO 9966919	ICM	A61K031-165
WO 9966919	ECLA	A61K031/167; A61K045/06
US 6160020	ECLA	A61K031/167; A61K045/06; C07C233/25

AB This invention relates to pharmaceutical compns. comprising an alkali or alkaline-earth metal salt of **acetaminophen** and at least one other active ingredient selected from the group consisting of analgesics, decongestants, expectorants, antitussives, antihistamines, gastrointestinal agents, diuretics, bronchodilators and mixts. thereof. The **acetaminophen** salts have both improved aqueous solubility and a less bitter taste than the free acid form of **acetaminophen**. A tablet contained **acetaminophen** calcium salt 368.23, chlorpheniramine maleate 2, microcryst. cellulose 520.77, Cab-O-Sil M5 4.5, and Mg stearate 4.5 mg.

ST tablet **acetaminophen** salt drug combination

IT Digestive tract
 (disease, agents for; pharmaceutical compns. containing **acetaminophen** salts and other drugs)

IT Drug delivery systems
 (oral; pharmaceutical compns. containing **acetaminophen** salts and other drugs)

IT Analgesics
 Antihistamines
 Antitussives
 Bronchodilators
 Decongestants
 Diuretics
 Drug bioavailability
 Expectorants
 (pharmaceutical compns. containing **acetaminophen** salts and other drugs)

IT Drug delivery systems
 (tablets; pharmaceutical compns. containing **acetaminophen** salts and other drugs)

IT 209967-42-0P 209967-44-2P 209967-45-3P
 209967-46-4P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(pharmaceutical compns. containing **acetaminophen** salts and other drugs)

IT 50-78-2, Acetylsalicylic acid 51-43-4, Epinephrine 51-55-8, Atropine, biological studies 53-86-1, Indomethacin 58-08-2, Caffeine, biological studies 58-55-9, Theophylline, biological studies 58-73-1, Diphenhydramine 59-33-6, Pyrillamine 59-42-7, Phenylephrine 60-87-7, Promethazine 68-88-2, Hydroxyzine 73-31-4 76-42-6, Oxycodone 76-57-3, Codeine 77-09-8, Phenolphthalein 77-19-0, Dicyclomine 77-22-5, Caramiphen 77-23-6, Carbetapentane 86-22-6, Brompheniramine 90-82-4, Pseudoephedrine 91-81-6, Tripeleminamine 93-14-1, Guaifenesin 103-90-2 104-31-4, Benzonatate 113-92-8, Chlorpheniramine maleate 125-29-1, Hydrocodone 125-69-9, Dextromethorphan hydrobromide 125-71-3, Dextromethorphan 128-62-1, Noscapine 129-03-3, Cyproheptadine 132-21-8, Dexbrompheniramine 147-24-0, Diphenhydramine hydrochloride 299-42-3, Ephedrine 317-34-0, Aminophylline 345-78-8, Pseudoephedrine hydrochloride 364-62-5, Metoclopramide 466-99-9, Hydromorphone 471-34-1, Calcium carbonate, biological studies 486-12-4, Triprolidine 554-10-9, 3-Iodo-1,2-propanediol 562-10-7, Doxylamine 586-06-1, Metaproterenol 606-04-2, Pamabrom 616-91-1, N-Acetylcysteine 642-72-8, Benzydamine 791-35-5, Chlophedianol 915-30-0, Diphenoxylate 2451-01-6, Terpin hydrate 3572-43-8, Bromhexine 3964-81-6, Azatadine 5104-49-4, Flurbiprofen 7020-55-5, Clidinium 7683-59-2, Isoprenaline 8024-48-4, Casanthranol 8050-81-5, Simethicone 12125-02-9, Ammonium chloride, biological studies 14838-15-4, Phenylpropanolamine 14882-18-9, Bismuth subsalicylate 15307-86-5, Diclofenac 15687-27-1 **16958-94-4** 18053-31-1, Fominoben 18559-94-9, Albuterol 18683-91-5, Ambroxol 21645-51-2, Aluminum hydroxide (Al(OH)₃), biological studies 22071-15-4, Ketoprofen 22204-53-1, Naproxen 23031-25-6, Terbutaline 25523-97-1, Dexchlorpheniramine **27203-92-5**, **Tramadol** 29679-58-1, Fenoprofen 29975-16-4, Estazolam 30392-40-6, Bitolterol 33005-95-7, Tiaprofenic acid 34580-13-7, Ketotifen **35719-43-8** 36322-90-4, Piroxicam 36950-96-6, Cicloprofen 38194-50-2, Sulindac 41340-25-4, Etodolac 42924-53-8, Nabumetone 50679-08-8, Terfenadine 51481-61-9, Cimetidine 51803-78-2 53179-11-6, Loperamide 53716-49-7, Carprofen 57644-54-9, Bismuth subcitrate 61869-07-6, Domiodol 66357-35-5, Ranitidine 68844-77-9, Astemizole 71125-38-7, Meloxicam 73590-58-6, Omeprazole 74103-06-3, Ketorolac 74978-16-8, Magaldrate 75970-99-9, Norastemizole 76824-35-6, Famotidine 76963-41-2, Nizatidine 79794-75-5, Loratidine 80937-31-1, Flosulide 82626-48-0, Zolpidem 83799-24-0, Fexofenadine 83881-51-0, Cetirizine 86181-42-2, Temelastine 87848-99-5, Acrivastine 169590-42-5, Celecoxib 180200-68-4 **209967-47-5** **209967-48-6** **209967-50-0** **209967-51-1**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(pharmaceutical compns. containing **acetaminophen** salts and other drugs)

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) Anon; 1996, 11, HCAPLUS
- (2) Anon; 1997, V1997(07)
- (3) Bottu; FR 2278324 A 1976 HCAPLUS
- (4) Kiyotaka, O; US 5409709 A 1995 HCAPLUS
- (5) Procter & Gamble; WO 9523595 A 1995 HCAPLUS
- (6) Rama Rao India; IN 172949 A HCAPLUS
- (7) SCR Newpharm; FR 2751875 A 1998 HCAPLUS
- (8) Schering Corp; EP 0396404 A 1990 HCAPLUS
- (9) Sunshine Abraham; WO 8504589 A 1985 HCAPLUS

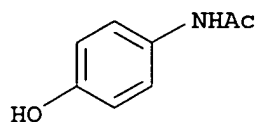
(10) Taisho Pharmaceut Co Ltd; JP 09-067256 A 1997 HCAPLUS

IT 209967-42-0P 209967-44-2P 209967-45-3P
209967-46-4P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pharmaceutical compns. containing **acetaminophen** salts and other drugs)

RN 209967-42-0 HCAPLUS

CN Acetamide, N-(4-hydroxyphenyl)-, monosodium salt, hexahydrate (9CI) (CA INDEX NAME)

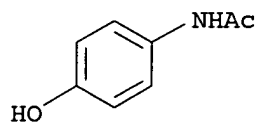


● Na

●6 H₂O

RN 209967-44-2 HCAPLUS

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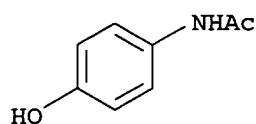


● Na

●7 H₂O

RN 209967-45-3 HCAPLUS

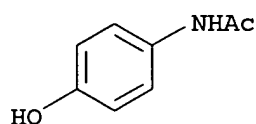
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● 1/2 Ca

● H₂O

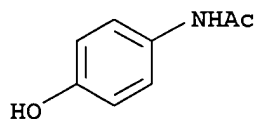
RN 209967-46-4 HCAPLUS
 CN Acetamide, N-(4-hydroxyphenyl)-, monolithium salt, hexahydrate (9CI) (CA INDEX NAME)



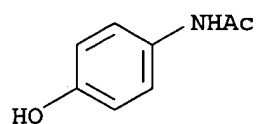
● Li

● 6 H₂O

IT 103-90-2 16958-94-4 27203-92-5,
 Tramadol 35719-43-8 209967-47-5
 209967-48-6 209967-50-0 209967-51-1
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (pharmaceutical compns. containing **acetaminophen** salts and other drugs)
 RN 103-90-2 HCAPLUS
 CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



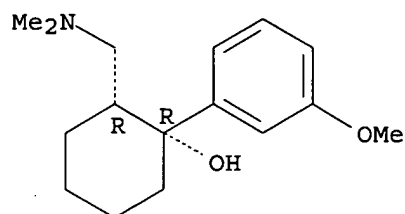
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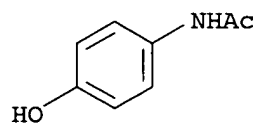
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RN 27203-92-5 HCAPLUS
 CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel-
 (9CI) (CA INDEX NAME)

Relative stereochemistry.

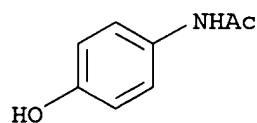


RN 35719-43-8 HCAPLUS
 CN Acetamide, N-(4-hydroxyphenyl)-, monopotassium salt (9CI) (CA INDEX NAME)



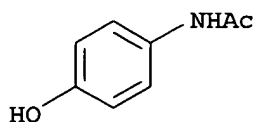
● K

RN 209967-47-5 HCAPLUS
 CN Acetamide, N-(4-hydroxyphenyl)-, calcium salt (2:1) (9CI) (CA INDEX NAME)



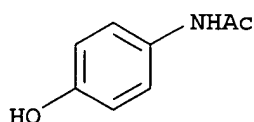
● 1/2 Ca

RN 209967-48-6 HCAPLUS
 CN Acetamide, N-(4-hydroxyphenyl)-, monolithium salt (9CI) (CA INDEX NAME)



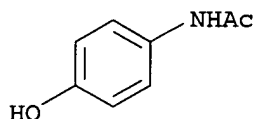
● Li

RN 209967-50-0 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)-, monocation salt (9CI) (CA INDEX NAME)



● Cs

RN 209967-51-1 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)-, magnesium salt (2:1) (9CI) (CA INDEX NAME)



● 1/2 Mg

L84 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:435283 HCAPLUS
DN 125:105766
ED Entered STN: 24 Jul 1996
TI Characterization of endothelin-induced nociception in mice: evidence for a mechanistically distinct analgesic model
AU Raffa, Robert B.; Schupsky, James J.; Lee, David K. H.; Jacoby, Henry I.
CS Drug Discovery, R. W. Johnson Pharm. Res. Inst., Spring House, PA, 19477-0776, USA
SO Journal of Pharmacology and Experimental Therapeutics (1996), 278(1), 1-7
CODEN: JPETAB; ISSN: 0022-3565
PB Williams & Wilkins
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
Section cross-reference(s): 1
AB The behavioral response elicited in mice by an i.p. injection of endothelin-1 (ET-1) (0.1 mg/kg) was differentiated from that elicited by

standard agents such as acetylcholine (ACh) (5.5 mg/kg) or phenyl-p-quinone (PpQ) (1.25 mg/kg). First, there was lack of two-way 'cross-tolerance' between test paradigms. I.e., at equieffective doses, a 60-min prior i.p. injection of ET-1 blocked the behavioral response to a subsequent i.p. injection of ET-1 or PpQ, but not of ACh, whereas a 60-min prior injection of ACh or of PpQ had no effect on a subsequent i.p. injection of ACh, PpQ or ET-1. Second, differential antagonism of ET-1-, ACh- or PpQ-induced responses was observed in an examination of 36 test compds. For example, cyclooxygenase inhibitors such as indomethacin and ibuprofen did not block the ET-1-induced response at >10 times the doses that blocked ACh- or PpQ-induced responses, whereas other compds. (such as certain benzodiazepines) inhibited ET-1-induced, but not ACh- or PpQ-induced, responses. These findings suggest that ET-1 produces a novel nociceptive stimulus, mechanistically distinct from ACh and PpQ. Hence, the ET-1-induced behavioral response in mice serves as a rapid and convenient measure of in vivo endothelin activity. In addition, this test might be a model for clin. pains not adequately treated by present analgesic agents or adequately tested by preclin. antinociceptive screens using ACh or PpQ. As such, it is a potentially valuable model for the identification of novel analgesic and other agents.

ST endothelin nociception analgesic screening

IT Analgesics

Drug tolerance

Pain

(endothelin-induced nociception in mice and mechanistically distinct analgesic and clin. pain model)

IT 50-06-6, Phenobarbital, biological studies 50-48-6, Amitriptyline
50-78-2, Aspirin 51-55-8, Atropine, biological studies 51-64-9,
d-Amphetamine 52-53-9, Verapamil 53-86-1, Indomethacin 57-27-2,
Morphine, biological studies 57-33-0 57-53-4, Meprobamate 58-25-3,
Chlordiazepoxide 59-46-1, Procaine 68-88-2, Hydroxyzine 76-57-3,
Codeine 92-13-7, Pilocarpine 103-90-2, **Acetaminophen**
137-58-6, Lidocaine 359-83-1, Pentazocine 439-14-5, Diazepam
1134-47-0, Baclofen 1622-62-4, Flunitrazepam 4199-09-1, (-)Propranolol
4205-90-7, Clonidine 15687-27-1, Ibuprofen 17617-23-1, Flurazepam
22204-53-1, Naproxen 27203-92-5, **Tramadol**
28911-01-5, Triazolam 28981-97-7, Alprazolam 35711-34-3, Tolmetin
sodium 42399-41-7, Diltiazem 64603-91-4, THIP 78123-71-4, DAMGO
111406-87-2, Zileuton 132746-60-2, CP 96345

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(analgesic screening in endothelin-induced nociception mechanistically distinct model in mice)

IT 51-84-3, Acetylcholine, biological studies 106-51-4, p-Quinone,
biological studies 123626-67-5, Endothelin-1

RL: ADV (Adverse effect, including toxicity); BUU (Biological use,
unclassified); BIOL (Biological study); USES (Uses)

(endothelin-induced nociception in mice and mechanistically distinct analgesic and clin. pain model)

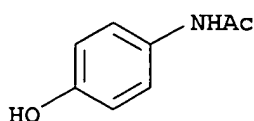
IT 103-90-2, **Acetaminophen** 27203-92-5,
Tramadol

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(analgesic screening in endothelin-induced nociception mechanistically distinct model in mice)

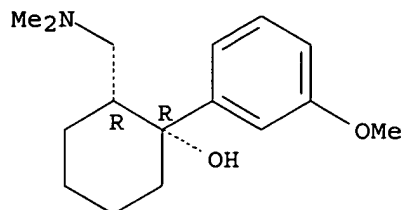
RN 103-90-2 HCAPLUS

CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



RN 27203-92-5 HCAPLUS
 CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel-
 (9CI) (CA INDEX NAME)

Relative stereochemistry.



L84 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1995:992320 HCAPLUS

DN 124:75606

ED Entered STN: 20 Dec 1995

TI Testing for synergism over a range of fixed ratio drug combinations:
 replacing the isobologram.

AU Tallarida, Ronald J.; Raffa, Robert B.

CS Dep. Pharmacol., Temple Univ. Sch. Med., Philadelphia, PA, 19140-5104, USA

SO Life Sciences (1995), 58(2), PL23-PL28

CODEN: LIFSAK; ISSN: 0024-3205

PB Elsevier

DT Journal

LA English

CC 1-4 (Pharmacology)

AB An isobologram is a Cartesian plot of pairs of doses that, in combination, yield a specified level of effect. It is a convenient and presently popular way of graphically displaying results of drug-combination and similar studies, because paired values of exptl. points that fall below or above the line connecting the axial points (usually ED50 values) denote supra- and sub-additive combinations, resp. However, an isobologram does not fulfill the criteria for standard least squares regression anal. It is thus less useful for addressing questions related to the range of combination ratios over which synergy occurs. We describe a substitute for the isobologram, in which log(total-dose) is plotted against the proportion of a component in a combination. One advantage is that a nonlinear curve-fitting procedure and determination of the confidence interval of

a single parameter allow the determination of departure from additivity over a range of fixed proportion mixts. An example is given of the combination of two analgesics (**acetaminophen** and **tramadol hydrochloride**). Another advantage of the new method is the reduction of animal use.

ST drug synergism math analysis

IT Pharmaceuticals

(testing for synergism over a range of fixed ratio drug combinations)

IT Statistics and Statistical analysis

(regression, testing for synergism over a range of fixed ratio drug combinations)

IT Drug interactions

(synergistic, testing for synergism over a range of fixed ratio drug combinations)

IT 147630-10-2, Acetaminophen-tramadol

hydrochloride mixture

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(testing for synergism over a range of fixed ratio drug combinations)

IT 147630-10-2, Acetaminophen-tramadol

hydrochloride mixture

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(testing for synergism over a range of fixed ratio drug combinations)

RN 147630-10-2 HCAPLUS

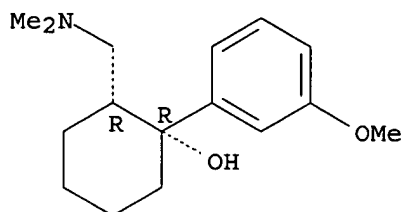
CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride (9CI) (CA INDEX NAME)

CM 1

CRN 36282-47-0

CMF C16 H25 N O2 . Cl H

Relative stereochemistry.

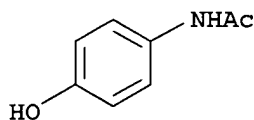


● HCl

CM 2

CRN 103-90-2

CMF C8 H9 N O2



L84 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 1994:612995 HCAPLUS
 DN 121:212995
 ED Entered STN: 29 Oct 1994
 TI Composition comprising a **tramadol** material and **acetaminophen** and its use
 IN **Raffa, Robert B.; Vaught, Jeffrey L.**
 PA **McNeilab, Inc., USA**
 SO U.S., 8 pp. Cont.-in-part of U.S. Ser. No. 755,924, abandoned.
 CODEN: USXXAM
 DT Patent
 LA English
 IC ICM A61K031-165
 NCL 514629000
 CC 63-6 (Pharmaceuticals)
 FAN.CNT 2

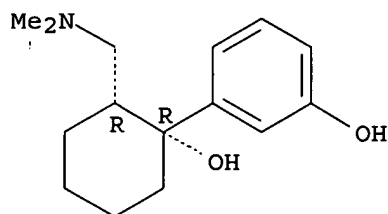
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5336691	A	19940809	US 1992-974865	19921110 <--
	CA 2095523	AA	19930307	CA 1992-2095523	19920903 <--
	CA 2095523	C	20040622		

HU 64838	A2	19940328	HU 1993-1313	19920903 <--
HU 219332	B	20010328		
AT 169498	E	19980815	AT 1992-919762	19920903 <--
ES 2120451	T3	19981101	ES 1992-919762	19920903 <--
RU 2121346	C1	19981110	RU 1993-43625	19920903 <--
SG 80535	A1	20010522	SG 1996-5733	19920903 <--
ZA 9207434	A	19940328	ZA 1992-7434	19920928 <--
CN 1086133	A	19940504	CN 1992-112594	19921024 <--
CN 1071571	B	20010926		
PRAI US 1991-755924	B2	19910906	<--	

CLASS

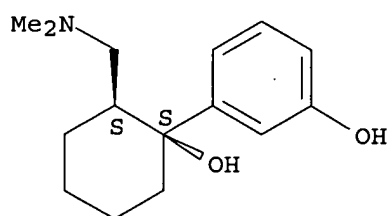
PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 5336691	ICM	A61K031-165
	NCL	514629000
US 5336691	ECLA	A61K031/165+M
AB	This invention relates to a composition comprising tramadol or its various forms or salts and acetaminophen , and its use. The compns. are pharmacol. useful in treating pain and tissue conditions. The compns. are also subject to less opioid side-effects such a abuse liability, tolerance, constipation and respiratory depression. Furthermore, where the components of the compns. are within certain ratios the pharmacol. effects of the compns. are superadditive (synergistic).	
ST	tranadol acetaminophen analgesic	
IT	Analgesics Antihistaminics Antitussives Bronchodilators Hypnotics and Sedatives Muscle relaxants (analgesic acetaminophen-tramadol compns.)	
IT	144830-14-8P 144830-15-9P RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (analgesic acetaminophen-tramadol compns.)	
IT	103-90-2, Acetaminophen 27203-92-5, Tramadol 36282-47-0, Tramadol hydrochloride 147441-56-3, Tramadol N-oxide RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (analgesic acetaminophen-tramadol compns.)	
IT	148229-78-1, (+)-Tramadol 148229-79-2, (-)- Tramadol RL: RCT (Reactant); RACT (Reactant or reagent) (analgesic acetaminophen-tramadol compns.)	
IT	148218-19-3P RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (analgesic acetaminophen-tramadol compns.)	
IT	144830-14-8P 144830-15-9P RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (analgesic acetaminophen-tramadol compns.)	
RN	144830-14-8 HCAPLUS	
CN	Phenol, 3-[(1R,2R)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]- (9CI) (CA INDEX NAME)	

Absolute stereochemistry. Rotation (+).

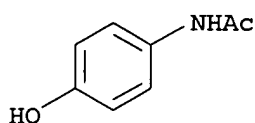


RN 144830-15-9 HCAPLUS
 CN Phenol, 3-[(1S,2S)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]- (9CI)
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

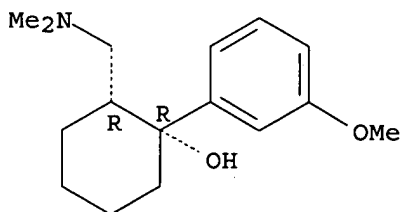


IT 103-90-2, Acetaminophen 27203-92-5,
 Tramadol 36282-47-0, Tramadol
 hydrochloride 147441-56-3, Tramadol N-oxide
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
 (Uses)
 (analgesic acetaminophen-tramadol compns.)
 RN 103-90-2 HCAPLUS
 CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



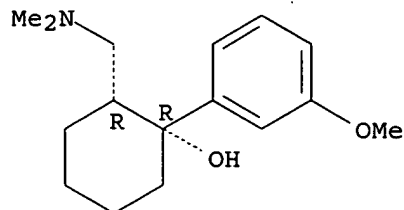
RN 27203-92-5 HCAPLUS
 CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel-
 (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 36282-47-0 HCAPLUS
 CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-,
 hydrochloride, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

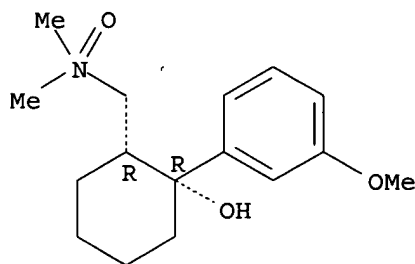


● HCl

RN 147441-56-3 HCAPLUS

CN Cyclohexanol, 2-[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



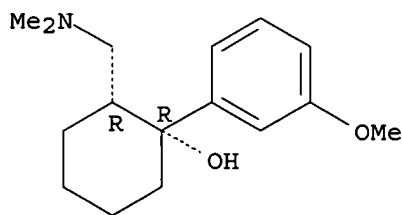
IT 148229-78-1, (+)-Tramadol 148229-79-2, (-)-
Tramadol

RL: RCT (Reactant); RACT (Reactant or reagent)
(analgesic acetaminophen-tramadol compns.)

RN 148229-78-1 HCAPLUS

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1R,2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



● HCl

RN 148229-79-2 HCAPLUS

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1S,2S)- (9CI) (CA INDEX NAME)

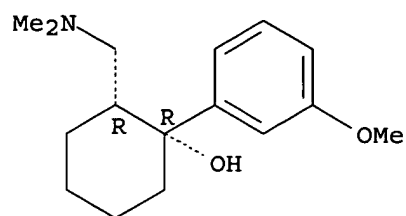
Absolute stereochemistry. Rotation (-).

CA 2095523	AA	19930307	CA 1992-2095523	19920903 <--
CA 2095523	C	20040622		
AU 9225799	A1	19930405	AU 1992-25799	19920903 <--
AU 651247	B2	19940714		
EP 566709	A1	19931027	EP 1992-919762	19920903 <--
EP 566709	B1	19980812		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, SE				
HU 64838	A2	19940328	HU 1993-1313	19920903 <--
HU 219332	B	20010328		
JP 06502869	T2	19940331	JP 1993-505447	19920903 <--
JP 3381190	B2	20030224		
AT 169498	E	19980815	AT 1992-919762	19920903 <--
ES 2120451	T3	19981101	ES 1992-919762	19920903 <--
RU 2121346	C1	19981110	RU 1993-43625	19920903 <--
SG 80535	A1	20010522	SG 1996-5733	19920903 <--
ZA 9207434	A	19940328	ZA 1992-7434	19920928 <--
CN 1086133	A	19940504	CN 1992-112594	19921024 <--
CN 1071571	B	20010926		
PRAI US 1991-755924	A	19910906	<--	
WO 1992-US7542	A	19920903		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9304675	ICM	A61K031-16
	ICS	A61K031-13
AB	Synergistic mixture of tramadol (I) and acetaminophen (II) are used for treatment of pain. The mixture has little opioid side-effects such as abuse, tolerance, constipation, and respiratory depression. A solution contained I 8, II 400 mg and water to 10 mL. The effects of the solution were studied in acetylcholine-induced abdominal constriction test in mice.	
ST	synergistic tramadol acetaminophen pharmaceutical pain	
IT	Analgesics	
	(tramadol-acetaminophen mixture, synergistic)	
IT	147630-09-9 147630-10-2 147657-25-8	
	147731-79-1 147731-80-4	
	RL: BIOL (Biological study)	
	(pharmaceutical composition containing, for treatment of pain)	
IT	27203-92-5P, Tramadol	
	RL: PREP (Preparation)	
	(preparation of, for N-oxide derivative preparation)	
IT	80456-81-1P, O-Desmethyl tramadol	
	RL: PREP (Preparation)	
	(preparation of, for treatment of pain)	
IT	147630-09-9 147630-10-2 147657-25-8	
	147731-79-1 147731-80-4	
	RL: BIOL (Biological study)	
	(pharmaceutical composition containing, for treatment of pain)	
RN	147630-09-9 HCAPLUS	
CN	Acetamide, N-(4-hydroxyphenyl)-, mixt. with rel-(1R,2R)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol (9CI) (CA INDEX NAME)	
CM	1	
CRN	27203-92-5	
CMF	C16 H25 N O2	

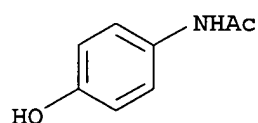
Relative stereochemistry.



CM 2

CRN 103-90-2

CMF C8 H9 N O2



RN 147630-10-2 HCAPLUS

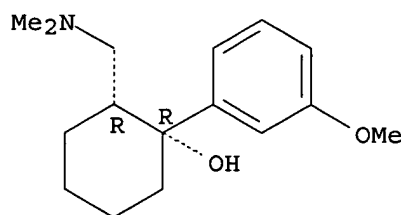
CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride (9CI) (CA INDEX NAME)

CM 1

CRN 36282-47-0

CMF C16 H25 N O2 . Cl H

Relative stereochemistry.

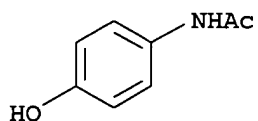


● HCl

CM 2

CRN 103-90-2

CMF C8 H9 N O2



RN 147657-25-8 HCAPLUS

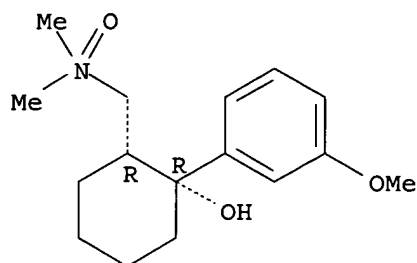
CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with cis-2-
[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)cyclohexanol (9CI) (CA
INDEX NAME)

CM 1

CRN 147441-56-3

CMF C16 H25 N O3

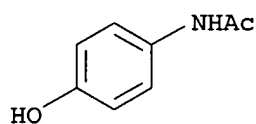
Relative stereochemistry.



CM 2

CRN 103-90-2

CMF C8 H9 N O2



RN 147731-79-1 HCAPLUS

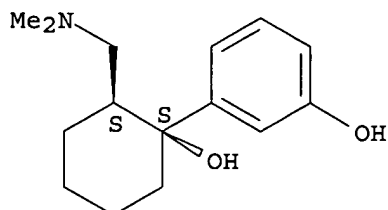
CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with (1S-cis)-3-[2-
[(dimethylamino)methyl]-1-hydroxycyclohexyl]phenol (9CI) (CA INDEX NAME)

CM 1

CRN 144830-15-9

CMF C15 H23 N O2

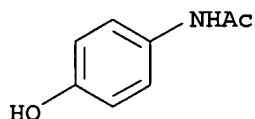
Absolute stereochemistry. Rotation (-).



CM 2

CRN 103-90-2

CMF C8 H9 N O2

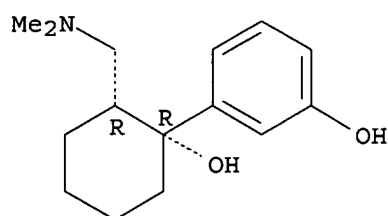


RN 147731-80-4 HCAPLUS
 CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with (1R-cis)-3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]phenol (9CI) (CA INDEX NAME)

CM 1

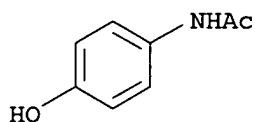
CRN 144830-14-8
 CMF C15 H23 N O2

Absolute stereochemistry. Rotation (+).



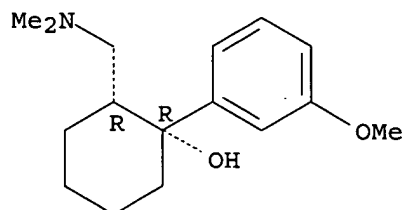
CM 2

CRN 103-90-2
 CMF C8 H9 N O2



IT **27203-92-5P, Tramadol**
 RL: PREP (Preparation)
 (preparation of, for N-oxide derivative preparation)
 RN 27203-92-5 HCAPLUS
 CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

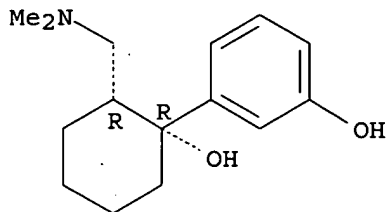
Relative stereochemistry.



IT **80456-81-1P, O-Desmethyl tramadol**
 RL: PREP (Preparation)
 (preparation of, for treatment of pain)
 RN 80456-81-1 HCAPLUS

CN Phenol, 3-[(1R,2R)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, rel-
(9CI) (CA INDEX NAME)

Relative stereochemistry.



=> => fil wpix

FILE 'WPIX' ENTERED AT 08:21:24 ON 06 APR 2005
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FILE LAST UPDATED: 1 APR 2005 <20050401/UP>
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=> d all abeq tech abex tot

L107 ANSWER 1 OF 4 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 2000-147173 [13] WPIX

DNC C2000-046031

TI Pharmaceutical composition comprising an isolated **acetaminophen**
salt and at least one other active agent, has improved analgesic ability.

DC B05

IN HIGGINS, J D; MARTELLUCCI, S A; NADIG, D; OHANNESIAN, L A; REY, M

PA (MCNI) MCNEIL-PPC INC

CYC 84

PI WO 9966919 A1 19991229 (200013)* EN 30 A61K031-165

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SL SZ UG ZW

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE
GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD
MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA

UG UZ VN YU ZA ZW

AU 9943380 A 20000110 (200025) A61K031-165

US 6160020 A 20001212 (200067) A61K031-16

ADT WO 9966919 A1 WO 1999-US13064 19990609; AU 9943380 A AU 1999-43380
19990609; US 6160020 A CIP of US 1996-771176 19961220, CIP of US
1997-987210 19971209, US 1998-100284 19980619

FDT AU 9943380 A Based on WO 9966919

PRAI US 1998-100284 19980619; US 1996-771176 19961220;

US 1997-987210 19971209

IC ICM A61K031-16; A61K031-165

ICS C07C233-00

AB WO 9966919 A UPAB: 20000313

NOVELTY - Pharmaceutical composition comprising an isolated
acetaminophen salt (I) and at least one other active agent
selected from analgesics, decongestants, expectorants, antitussives,
antihistamines, gastrointestinal agents, diuretics and/or bronchodilators,
is new.

DETAILED DESCRIPTION - Pharmaceutical composition comprises an
isolated **acetaminophen** salt of formula (I) and at least one
other active agent selected from analgesics, decongestants, expectorants,
antitussives, antihistamines, gastrointestinal agents, diuretics and/or
bronchodilators.

n = 1 or 2;

M = alkali metal when n is 1 and M is alkaline earth metal when n is
2; and

x = 0-10.

ACTIVITY - Analgesic; antipyretic.

MECHANISM OF ACTION - None given.

USE - The composition is used to elicit onset of hastened analgesic
or antipyretic response (claimed).

ADVANTAGE - (I) have significantly increased dissolution rates
compared to the conventional free acid form of **acetaminophen**.

(I) have improved taste compared to the conventional form of
acetaminophen. The increased solubility results in faster peak
acetaminophen plasma concentration which will potentially provide
faster onset of action of the analgesic and/or antipyretic activity. In a
test using 0.1 N HCl and a USP Dissolution Apparatus 2 (paddle speed: 50
rpm) at 37 deg. C, the concentration of **acetaminophen** at 30 s
was 0.30 mg/ml for **acetaminophen** sodium salt, 0.32 mg/ml for
acetaminophen lithium salt and 0.20 mg/ml for
acetaminophen calcium salt, cf. 0.02 mg/ml for the free acid
(control).

Dwg.0/2

FS CPI

FA AB; GI; DCN

MC CPI: B05-A01A; B05-A01B; B05-C01; B06-H; B07-H; B14-C01; B14-E10;
B14-J01B1; B14-K01B; B14-K01D; B14-K01E; B14-L09; B14-N08

TECH UPTX: 20000313

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The alkali
metal is selected from Na, K, Cs and Li. The alkaline earth metal is
selected from Ca and Mg. (I) is in hydrated or anhydrous form. The
analgesic is selected from e.g. acetyl salicylic acid, indomethacin,
ibuprofen (racemates or optically active isomers), naproxen, flurbiprofen
sulindac or codeine. The decongestant is selected from pseudoephedrine,
phenylpropanolamine, phenylephrine and ephedrine. The expectorant is
selected from e.g. guaifenesin, ambroxol and domiodol. The antitussive is
selected from e.g. dextromethorphan, caramiphen and bezonatate. The
antihistamine is selected from e.g. brompheniramine, fexofenadine and
loratidine. The gastrointestinal agent is selected from e.g. atropine,
clidinium and dicyclomine. The diuretic is selected from caffeine and
pamabrom. The bronchodilator is selected from e.g. terbutaline, pinephrine
and isoprenaline. The sleep-inducing agent is selected from e.g.
melatonin, estazolam and zolpidem.

ABEX UPTX: 20000313

ADMINISTRATION - Administration may be oral and in a dose of 80-1000 mg (**acetaminophen** free acid basis).

L107 ANSWER 2 OF 4 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 1996-251055 [25] WPIX

CR 1993-190047 [24]

DNC C1996-079425

TI Compsn. for treating pain or as an antitussive - comprises ibuprofen and **tramadol**.

DC B05

IN **RAFFA, R B**

PA (MCNI) **MCNEILAB INC**

CYC 1

PI US 5516803 A 19960514 (199625)* 7 A61K031-19

ADT US 5516803 A CIP of US 1991-785137 19911030, Cont of US 1992-974863 19921110, US 1995-397022 19950301

PRAI US 1992-974863 19921110; US 1991-785137 19911030;
US 1995-397022 19950301

IC ICM A61K031-19

ICS A61K031-135

AB US 5516803 A UPAB: 19960625

Compsn. comprises a **tramadol** material (I) and ibuprofen (II) in a weight ratio of 1:1-200.

The comps. pref. further comprises a carrier, an antitussive, a muscle relaxant, a deep and a decongestant or bronchodilation and or an antihistamine (opt. non-sedating).

USE - The compsns. are used as antitussive and to control pain. They may also contain other ingredients e.g. decongestants, bronchodilators, antitussives, antihistamines of muscle relaxants or may be combined with **tramadol/acetaminophen** formulations for treating allergies, sleep disorders, cold, cough, cold-like and/or flu symptoms.

ADVANTAGE - The compsns. have less opioid side-effects such as abuse liability, tolerance, constipation and respiratory depression. (I) and (II) are synergistic.

Dwg.0/1

FS CPI

FA AB; DCN

MC CPI: B10-B03B; B10-C04C; B14-C01; B14-C03; B14-K01B

L107 ANSWER 3 OF 4 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 1994-255297 [31] WPIX

CR 1993-100637 [12]

DNC C1994-116765

TI Synergistic combination of a **tramadol** material and **acetaminophen** - for treating pain and tussive conditions, has fewer side effects than when each component is used alone..

DC B05

IN **RAFFA, R B; VAUGHT, J L**

PA (MCNI) **MCNEILAB INC**

CYC 1

PI US 5336691 A 19940809 (199431)* 8 A61K031-165

ADT US 5336691 A CIP of US 1991-755924 19910906, US 1992-974865 19921110

PRAI US 1991-755924 19910906; US 1992-974865 19921110

IC ICM A61K031-165

AB US 5336691 A UPAB: 19940921

A pharmaceutical comps. comprises a **tramadol** substance and **acetaminophen** in weight ratio 1:1-1:1600.

The **tramadol** is **tramadol** hydrochloride, which is especially racemic. The weight ratio **tramedol**:**aminoacetophen** is 1:5-1:1600, especially 1:19-1:800, especially pref. 1:19-1:50.

USE/ADVANTAGE - The combination can be used to treat pain and tussive

conditions. Suitable daily doses are 10-6000 mg/kg active ingredients. The mixture is synergistic and smaller amts. of each component can be used than when they are used alone thus the risk of side effects is reduced. The compsns. are subject to less opioid side-effects such as abuse liability, tolerance, constipation and respiratory depression.

Dwg.0/1

FS CPI

FA AB; DCN

MC CPI: B10-B03B; B10-E02; B14-C01; B14-N17; B14-S09

L107 ANSWER 4 OF 4 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 1993-100637 [12] WPIX

CR 1994-255297 [31]

DNC C1993-044353

TI Synergistic combination of **tramadol** and **acetaminophen**
- for treating pain and tissue conditions.

DC B05

IN **RAFFA, R B; VAUGHT, J L**

PA (MCNI) **MCNEILAB INC;** (ORTH) **ORTHO-MCNEIL PHARM INC;**
(JOHJ) **JOHNSON & JOHNSON**

CYC 42

PI WO 9304675 A1 19930318 (199312)* EN 19 A61K031-16
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA SE
W: AU BB BG BR CA FI HU JP KP KR LK MG MW NO RO RU SD
AU 9225799 A 19930405 (199330) A61K031-165
EP 566709 A1 19931027 (199343) EN A61K031-16
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL SE
HU 64838 T 19940328 (199417) A61K031-16
JP 06502869 W 19940331 (199418) A61K031-135
ZA 9207434 A 19940525 (199423)# 19 A61K000-00
AU 651247 B 19940714 (199432) A61K031-165
NZ 244507 A 19940927 (199438)# A61K031-165
TW 242562 A 19950311 (199521) A61K031-135
CN 1086133 A 19940504 (199528) A61K031-165
EP 566709 A4 19940406 (199530) A61K031-16
IL 103313 A 19970610 (199730)# A61K031-13
EP 566709 B1 19980812 (199836) EN A61K031-16
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL SE
DE 69226624 E 19980917 (199843) A61K031-16
ES 2120451 T3 19981101 (199851) A61K031-16
CN 1198929 A 19981118 (199914)# A61K031-165
PH 29613 A 19960415 (200012)# A61K031-165
RU 2121346 C1 19981110 (200013) A61K031-085
MX 187871 B 19980123 (200046)# A61K031-005
KR 243956 B1 20000302 (200122) A61K031-13
HU 219332 B 20010328 (200124) A61K031-16
SG 80535 A1 20010522 (200134) A61K031-16
JP 3381190 B2 20030224 (200317) 11 A61K031-135
CA 2095523 C 20040622 (200442) EN A61K031-505
CN 1071571 C 20010926 (200509)# A61K031-166

ADT WO 9304675 A1 WO 1992-US7542 19920903; AU 9225799 A AU 1992-25799
19920903; EP 566709 A1 EP 1992-919762 19920903; WO 1992-US7542 19920903;
HU 64838 T WO 1992-US7542 19920903; HU 1993-1313 19920903; JP 06502869 W
WO 1992-US7542 19920903; JP 1993-505447 19920903; ZA 9207434 A ZA
1992-7434 19920928; AU 651247 B AU 1992-25799 19920903; NZ 244507 A NZ
1992-244507 19920925; TW 242562 A TW 1992-108965 19921110; CN 1086133 A CN
1992-112594 19921024; EP 566709 A4 EP 1992-919762 ; IL 103313 A IL
1992-103313 19921001; EP 566709 B1 EP 1992-919762 19920903; WO 1992-US7542
19920903; DE 69226624 E DE 1992-626624 19920903; EP 1992-919762 19920903;
WO 1992-US7542 19920903; ES 2120451 T3 EP 1992-919762 19920903; CN 1198929
A Div ex CN 1992-112594 19921024; CN 1998-107417 19980420; PH 29613 A PH
1993-45661 19930202; RU 2121346 C1 RU 1993-43625 19920903; MX 187871 B MX
1992-5702 19921005; KR 243956 B1 WO 1992-US7542 19920903; KR 1993-701352

19930506; HU 219332 B WO 1992-US7542 19920903, HU 1993-1313 19920903; SG 80535 A1 SG 1996-5733 19920903; JP 3381190 B2 WO 1992-US7542 19920903, JP 1993-505447 19920903; CA 2095523 C CA 1992-2095523 19920903, WO 1992-US7542 19920903; CN 1071571 C CN 1992-112594 19921024

FDT AU 9225799 A Based on WO 9304675; EP 566709 A1 Based on WO 9304675; HU 64838 T Based on WO 9304675; JP 06502869 W Based on WO 9304675; AU 651247 B Previous Publ. AU 9225799, Based on WO 9304675; EP 566709 B1 Based on WO 9304675; DE 69226624 E Based on EP 566709, Based on WO 9304675; ES 2120451 T3 Based on EP 566709; HU 219332 B Previous Publ. HU 64838, Based on WO 9304675; JP 3381190 B2 Previous Publ. JP 06502869, Based on WO 9304675; CA 2095523 C Based on WO 9304675

PRAI US 1991-755924 19910906; ZA 1992-7434 19920928;
 NZ 1992-244507 19920925; IL 1992-103313 19921001;
 CN 1998-107417 19980420; PH 1993-45661 19930202;
 MX 1992-5702 19921005

REP 1.Jnl.Ref; US 3652589; No-Citns.

IC ICM A61K000-00; A61K031-005; A61K031-085; A61K031-13; A61K031-135;
 A61K031-16; A61K031-165; A61K031-166; A61K031-505
 ICS A61K031-167; A61K031-485; A61P025-04; A61P029-02

ICA C07C217-54

AB WO 9304675 A UPAB: 20050207
 New compsn. comprises a **tramadol** (I) material,
acetaminophen (II) and opt. a carrier.
 Pref. (I) material includes (I), its N-oxide and O-desmethyl derivs.
 and mixts. of these; isomers, mixts of these and racemates; and salts,
 solvates and polymorphs. Racemic (I HCl) is pref. (I) is described in US
 Pat. 3,652,589.
 USE/ADVANTAGE - The compsn. is analgesic and is useful for treatment
 of pain and tussive conditions. An effective dose requires less of both
 (I) and (II) than when using (I) or (II) alone, with a corresp. reduction of
 side effects (including opioid side effects (e.g. abuse liability,
 toleration, constipation and respiratory depression)). Certain ratios of
 (I) and (II) are synergistic.
 Admin. is oral or parenteral at a unit dose containing 0.1-800 mg/kg,
 pref. 0.3-200 mg/kg active ingredients.ti
 Dwg.0/1
 Dwg.0/1

FS CPI
 FA AB; DCN
 MC CPI: B10-A03; B10-B03B; B10-D03; B12-C09; B12-D01; B12-K01
 ABEQ EP 566709 A UPAB: 19931207
 New compsn. comprises a **tramadol** (I) material,
acetaminophen (II) and opt. a carrier.
 Pref. (I) material includes (I), its N-oxide and O-desmethyl derivs.
 and mixts. of these; isomers, mixts of these and racemates; and salts,
 solvates and polymorphs. Racemic (I HCl) is pref. (I) is described in US
 Pat. 3,652,589.
 USE/ADVANTAGE - The compsn. is analgesic and is useful for treatment
 of pain and tussive conditions. An effective dose requires less of both
 (I) and (II) than when using (I) or (II) alone, with a corresp. redn. of
 side effects (including opioid side effects (e.g. abuse liability,
 toleration, constipation and respiratory depression)). Certain ratios of
 (I) and (II) are synergistic.
 Admin. is oral or parenteral at a unit dose contg. 0.1-800 mg/kg,
 pref. 0.3-200 mg/kg active ingredients.

=> => fil uspatful

FILE 'USPATFULL' ENTERED AT 08:26:20 ON 06 APR 2005

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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 5 Apr 2005 (20050405/PD)

FILE LAST UPDATED: 5 Apr 2005 (20050405/ED)

HIGHEST GRANTED PATENT NUMBER: US6877166
 HIGHEST APPLICATION PUBLICATION NUMBER: US2005071904
 CA INDEXING IS CURRENT THROUGH 5 Apr 2005 (20050405/UPCA)
 ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 5 Apr 2005 (20050405/PD)
 REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2005
 USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2005

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 >>> <<<
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 >>> classifications, or claims, that may potentially change from <<<
 >>> the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d bib abs kwic hitstr tot

L117 ANSWER 1 OF 10 USPATFULL on STN

AN 2002:112901 USPATFULL
 TI Analgesic and glucosamine compositions
 IN **Raffa, Robert**, Norristown, PA, UNITED STATES
 Cowan, Alan, Ambler, PA, UNITED STATES
 Tallarida, Ronald, Mantua, NJ, UNITED STATES
 PA Temple University of the Commonwealth of Higher
 corporation)
 PI US 2002058642 A1 20020516
 AI US 2001-964178 A1 20010925 (9)
 PRAI US 2000-235405P 20000926 (60)
 DT Utility
 FS APPLICATION
 LREP Robert L. Andersen, Ratner & Prestia, One Westlakes, Berwyn, Suite 301,
 P.O. Box 980, Valley Forge, PA, 19482-0980
 CLMN Number of Claims: 16
 ECL Exemplary Claim: 1
 DRWN 3 Drawing Page(s)
 LN.CNT 678

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to a composition comprising a glucosamine
 material and an analgesic compound such as a nonsteroidal
 anti-inflammatory drug (NSAID) and/or an opioid analgesic and its use
 for treatment of pain in pharmaceutical or veterinary applications. When
 the components of the compositions are administered within certain
 ratios, the analgesic efficacy of the composition is super-additive
 (synergistic) relative to the analgesic efficacy of the analgesic
 compound alone.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IN **Raffa, Robert**, Norristown, PA, UNITED STATES

*There may be some
 "false" hits in
 this set -> full
 text file*

SUMM [0003] Drugs such as aspirin, ibuprofen, **acetaminophen**, and morphine are used as analgesics. Ibuprofen, aspirin and other analgesic nonsteroidal anti-inflammatory drugs (commonly referred to as NSAIDs) and **acetaminophen** are only useful in relieving pain of moderate intensity, whereas opioid analgesics such as morphine are useful in relieving more intense pain. However, opioids exhibit side-effects including addictive properties, and ibuprofen, aspirin, other NSAIDs and **acetaminophen** can cause serious gastrointestinal, renal, and cardiovascular side effects, especially when used in high doses and/or over long periods of. . .

SUMM . . . ratios. A. Pircio et al., Arch. Int. Pharmacodyn., 235,116 (1978) report that a mixture of butorphanol (an opioid analgesic) with **acetaminophen** (a non-opioid analgesic) in a 1:125 ratio yielded super-additive analgesia, but that a 1:10 mixture of the same components yielded merely additive analgesic effects. A combination of tolmetin (an NSAID) with **acetaminophen** (a non-opioid analgesic) has been reported to enable a marked reduction in the amount of tolmetin required to produce analgesia. . .

SUMM . . . the contrary, it has been shown that when glucosamine is combined at certain ratios, for example with aspirin, diclofenac or **tramadol** (a centrally acting non-opioid analgesic), the analgesic efficacy of analgesic is reduced (i.e., the combination is sub-additive) by as much. . .

SUMM . . . analgesic effects which can occur when two or more analgesics are combined or when an analgesic, such as diclofenac or **tramadol**, is combined with glucosamine. In the preferred embodiment, the combination of glucosamine with an analgesic compound at an appropriate ratio. . .

DETD Preparation of the Combined Doses of Glucosamine and **Tramadol**

DETD [0028] Solutions of glucosamine/**tramadol** combinations with different ratios were prepared and concentrations of each component expressed as mg per 10 mL of distilled water. For example, 250 mg of glucosamine sulfate and 10 mg of **tramadol** HCL were added to 10 mL of water with 2 drops of TWEEN®-80, a pharmacological dispersant, to yield a glucosamine sulfate to **tramadol** weight ratio of 25:1 (250 mg: 10 mg), which corresponds to a glucosamine to **tramadol** weight ratio of about 15:1.

DETD Preparation of the Combined Doses of Glucosamine and **Acetaminophen**

DETD [0029] Solutions of glucosamine/**acetaminophen** combinations with different ratios were prepared and concentrations of each component expressed as mg per 10 mL of distilled water. For example, 112.5 mg of glucosamine sulfate and 112.5 mg of **acetaminophen** were added to 10 mL of water with 2 drops of TWEEN®-80, a pharmacological dispersant, to yield a glucosamine sulfate to **acetaminophen** weight ratio 1:1 (112.5 mg:112.5 mg), which corresponds to a glucosamine to **acetaminophen** weight ratio of about 0.58:1.

DETD . . . were all dosed orally with glucosamine sulfate, which was completely dissolved in distilled water, and a selected analgesic (ibuprofen, diclofenac, **tramadol** HCL, or **acetaminophen**), which was completely dissolved in distilled water or in distilled water containing 2% by volume of TWEEN®-80 containing 100% polysorbate. . .

DETD [0043] Table 4 shows the results of assays of combinations of aspirin and glucosamine sulfate, **acetaminophen** and glucosamine sulfate, diclofenac and glucosamine sulfate, **tramadol** HCL and glucosamine sulfate, and indomethacin and glucosamine sulfate. Treatment doses were selected based on the ED50 for each analgesic. . .

DETD [0045] For **acetaminophen** alone compared **acetaminophen** in combination with glucosamine sulfate, the data demonstrate that **acetaminophen** does not exhibit a super-additive analgesic effect in combination with glucosamine sulfate, in general appears to exhibit sub-additive analgesia, but. . .

DETD [0046] Similarly, when either diclofenac or tramadol HCl was combined with glucosamine sulfate, the analgesic efficacy of either analgesic compound was substantially reduced at the ratios tested.. . when administered in combination with glucosamine sulfate at the concentrations tested, a clear case of sub-additivity. As another example, when tramadol HCl was used in combination with glucosamine sulfate, the analgesic efficacy of tramadol HCl was reduced such that the 50% effect level (5/10 animals protected) could not be achieved even with the combination containing 10 mg/kg of tramadol HCl, a tramadol HCl dosage greater than the ED50=8.05 mg/kg value of tramadol HCl when used alone, i.e., another clear case of sub-additivity. Thus, combinations of glucosamine with aspirin, acetaminophen, diclofenac or tramadol at those ratios are sub-additive and thus are, by definition, excluded from the scope of the invention. . .

DETD	mg/kg.sup.(a)	
ASA	Glucosamine	No. protected/no. tested
50	--	1/10
100	--	4/10
150	--	8/10
200	--	7/10
50	125	2/10
100	250	2/10
150	375	1/10
200	500	2/10

Acetaminophen, mg/kg + Glucosamine sulfate, mg/kg		
Acetaminophen	Glucosamine	No. protected/no. tested
62.5	--	1/10
125	--	4/10
250	--	8/10
28.12	28.12	1/10
56.25	56.25	2/10
62.5	62.5	1/10
93.75	93.75	0/10
112.5	112.5	5/10
125. . . . 50	5/10	
25	100	0/10
50	200	0/10
100	400	1/10

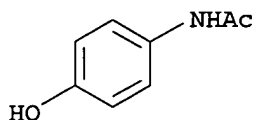
Diclofenac, mg/kg + Glucosamine sulfate, mg/kg.sup.(b)		
Diclofenac	Glucosamine	No. protected/no. tested
1.144	125	5/20
2.288	250	6/10

Tramadol HCl, mg/kg + Glucosamine sulfate, mg/kg.sup.(c)		
Tramadol	Glucosamine	No. protected/no. tested
6	150	1/10
10	250	3/10

Indomethacin, mg/kg + Glucosamine sulfate, mg/kg.sup.(d)		
Indomethacin	Glucosamine	No. protected/no. tested
2.5	--	4/10

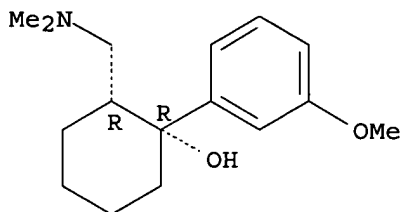
5.0. . . .		
IT	66-84-2, Glucosamine hydrochloride	103-90-2, Acetaminophen
	3416-24-8, Glucosamine	7512-17-6, N-Acetylglucosamine
	15307-86-5, Diclofenac	15687-27-1, Ibuprofen
		22071-15-4, Ketoprofen

27203-92-5, Tramadol 29031-19-4, Glucosamine sulfate
 (analgesic and glucosamine compns.)
 IT 103-90-2, Acetaminophen 27203-92-5, Tramadol
 (analgesic and glucosamine compns.)
 RN 103-90-2 USPATFULL
 CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



RN 27203-92-5 USPATFULL
 CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel-
 (9CI) (CA INDEX NAME)

Relative stereochemistry.



L117 ANSWER 2 OF 10 USPATFULL on STN

AN 1998:39530 USPATFULL

TI **Acetaminophen** and dimenhydrinate analgesics

IN Hough, Douglas R., Morrisville, PA, United States

Nelson, Edward B., Lower Gwynedd, PA, United States

Raffa, Robert B., Norristown, PA, United States

PA McNeil-PPC, Inc., Skillman, NJ, United States (U.S. corporation)

PI US 5739139 19980414

AI US 1996-667054 19960620 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Reamer, James H.

CLMN Number of Claims: 13

ECL Exemplary Claim: 1

DRWN 1 Drawing Figure(s); 1 Drawing Page(s)

LN.CNT 317

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed are compositions comprising **acetaminophen** (APAP) and dimenhydrinate and methods for their use in analgesia. When **acetaminophen** and dimenhydrinate are within certain ratios, their pharmacological effects are superadditive.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI **Acetaminophen** and dimenhydrinate analgesics

IN **Raffa, Robert B.**, Norristown, PA, United States

AB Disclosed are compositions comprising **acetaminophen** (APAP) and dimenhydrinate and methods for their use in analgesia. When **acetaminophen** and dimenhydrinate are within certain ratios, their pharmacological effects are superadditive.

SUMM The present invention relates to analgesic compositions. More particularly, the present invention relates to analgesic compositions containing **acetaminophen** and dimenhydrinate.

SUMM **Acetaminophen, N-(4-hydroxyphenyl)**
acetamide or herein referred to as APAP, was first used in
 medicine by Van Mering in 1893, but only since 1949. . . .

SUMM . . . when combined with APAP or aspirin exhibit superadditive
 antiarthritic activity. Also, U.S. Pat. No. 5,336,691 discloses that the
 combination of **tramadol**, a centrally active analgesic, and
 APAP exhibits a synergistic analgesic effect when combined in certain
 ratios. G. B. Pat. No. . . .

DETD (a) an analgesic inducing amount of **acetaminophen**;
 DETD . . . from about 1/20 to about 1/500 parts by weight dimenhydrinate
 or pharmaceutically acceptable salt thereof for each part by weight
acetaminophen; and

DETD . . . In a preferred embodiment of the present invention, the
 dimenhydrinate is present only to enhance the analgesic effect of the
acetaminophen. In such case, the dimenhydrinate should be
 present in an amount insufficient to produce substantial relief from
 motion sickness or. . . .

DETD TABLE 1

Mouse Acetylcholine-Bromide Induced
 Abdominal Constriction Assay

Acetaminophen (APAP) and HCl salt of Dimenhydrinate (DMHD)

Dose # of mice ED.sub.50 at 30 min
 (mg/kg, p.o.)

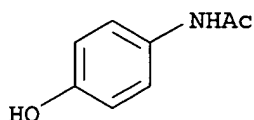
with no (95%. . . .

CLM What is claimed is:

1. A composition for use as an analgesic comprising: (a) an analgesic inducing amount of **acetaminophen**; (b) from about 1/20 to about 1/500 parts by weight dimenhydrinate or pharmaceutically acceptable salt thereof for each part by weight **acetaminophen**; and (c) a pharmaceutically acceptable carrier.
- . . . from about 1/50 to about 1/200 parts by weight dimenhydrinate or pharmaceutically acceptable salt thereof for each part by weight **acetaminophen**.
- . . . claim 1 which comprises about 1/100 parts by weight dimenhydrinate or pharmaceutically acceptable salt thereof for each part by weight **acetaminophen**.
4. The composition of claim 1 in a dosage form containing 10 to 2000 mg of **acetaminophen**.
5. The composition of claim 1 in a dosage form containing 25 to 1000 mg of **acetaminophen**.
6. The composition of claim 1 in a dosage form containing 100 to 500 mg of **acetaminophen**.
8. The composition of claim 1 which contains a sufficient amount of surface active agent to stabilize a suspension of the **acetaminophen**.
- . . . for inducing analgesia in a mammal comprising the step of administering a combination comprising: (a) an analgesic inducing amount of **acetaminophen**; (b) from about 1/20 to about 1/500 parts by weight dimenhydrinate or pharmaceutically acceptable salt thereof for each part by weight **acetaminophen**; and (c) a pharmaceutically acceptable carrier.
- . . . from about 1/50 to about 1/200 parts by weight dimenhydrinate or pharmaceutically acceptable salt thereof for each part by weight **acetaminophen**.

wherein said combination comprises about 1/100 parts by weight dimenhydrinate or pharmaceutically acceptable salt thereof for each part by weight **acetaminophen**.

IT 103-90-2, Acetaminophen 523-87-5, Dimenhydrinate
(synergistic analgesic combination containing acetaminophen and dimenhydrinate)
IT 103-90-2, Acetaminophen
(synergistic analgesic combination containing acetaminophen and dimenhydrinate)
RN 103-90-2 USPATFULL
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



L117 ANSWER 3 OF 10 USPATFULL on STN

AN 96:41241 USPATFULL
TI Composition comprising a **tramadol** material and a non-steroidal anti-inflammatory drug
IN **Raffa, Robert B.**, Norristown, PA, United States
PA McNeilab, Inc., Spring House, PA, United States (U.S. corporation)
PI US 5516803 19960514
AI US 1995-397022 19950301 (8)
RLI Continuation of Ser. No. US 1992-974863, filed on 10 Nov 1992, now abandoned which is a continuation-in-part of Ser. No. US 1991-785137, filed on 30 Oct 1991, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Henley, III, Raymond
LREP Palo, Ralph R.
CLMN Number of Claims: 15
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 552
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a composition comprising a **tramadol** material and a nonsteroidal antiinflammatory drug, and its use. The compositions are pharmacologically useful in treating pain and tussive conditions. The compositions are also subject to less opioid side-effects such as abuse liability, tolerance, constipation and respiratory depression. Furthermore, where the components of the compositions are within certain ratios the pharmacological effects of the compositions are superadditive (synergistic).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Composition comprising a **tramadol** material and a non-steroidal anti-inflammatory drug
IN **Raffa, Robert B.**, Norristown, PA, United States
AB This invention relates to a composition comprising a **tramadol** material and a nonsteroidal antiinflammatory drug, and its use. The compositions are pharmacologically useful in treating pain and tussive conditions.
SUMM . . . of analgesic cycloalkanol-substituted phenol esters having a basic amine group in the cycloalkyl ring. The compound (1R, 2R or 1S, 2S)-2-[(**dimethylamino**)methyl]-1-(3-methoxyphenyl)-cyclohexanol, commonly

known as **tramadol**, is specifically disclosed therein. A series of articles pertaining to the pharmacology, toxicology and clinical studies of **tramadol** are found in *Arzneim, Forsch. (Drug Res.)*, 28(I), 114 (1978). Driessen et al., *Arch. Pharmacol.*, 341, R104 (1990) disclose that **tramadol** produces its analgesic effect through a mechanism that is neither fully opioid-like nor non-opioid-like. The Abstracts of the VIth World Congress on Pain, Apr. 1-6 (1990), disclose that **tramadol** hydrochloride is an orally active pure agonist opioid analgesic. However, clinical experience indicates that **tramadol** lacks many of the typical side effects of opioid agonists, e.g., respiratory depression (W. Vogel et al., *Arzneim Forsch. (Drug Res.)*, 28(I), 158 (1978)). When given at a dose of 50 mg by rapid i.v. injection, **tramadol** may produce certain side effects unique to **tramadol** including hot flushes and sweating. Despite these side effects, **tramadol**'s combination of non-opioid and opioid activity makes **tramadol** a very unique drug. **Tramadol** is currently being marketed by Grunenthal GMBH as an analgesic.

- SUMM As alternatives to using opioids, non-opioids such as **acetaminophen**, aspirin and ibuprofen are used as analgesics. Ibuprofen, like aspirin, is not subject to the tolerance, addiction and toxicity of. . . .
- SUMM . . . al., *Arch. Int. Pharmacodyn.*, 235, 116 (1978) report superadditive analgesia with a 1:125 mixture of butorphanol, another opioid analgesic, and **acetaminophen**, a non-opioid analgesic, whereas a 1:10 mixture did not show any statistically significant superadditive analgesia.
- SUMM . . . *Int. J. Clin. Pharmacol. Biopharmacy*, 17, 250 (1979) report that the combination of non-opioid analgesics, i.e., tolmetin (another NSAID) and **acetaminophen**, allows for a marked reduction in the amount of tolmetin required to produce analgesia. In addition, U.S. Pat. No. 4,260,629 discloses that an orally administered composition of **acetaminophen** and zomepirac, a non-opioid analgesic, in a particular weight ratio range produces a superadditive relief of pain in mammals. Furthermore, U.S. Pat. No. 4,132,788 discloses that 5-aroyl-1-(lower)alkylpyrrole-2-acetic acid derivatives, non-opioid analgesics, when combined with **acetaminophen** or aspirin exhibit superadditive antiarthritic activity. However, there have been warnings against the daily consumption of non-opioid analgesic mixtures and. . . .
- SUMM The prior art, however, does not disclose that **tramadol**, an `atypical` opioid analgesic, can or should be combined with another analgesic to lessen the side effects of each or to yield a composition comprising a **tramadol** material and another analgesic that exhibits superadditive analgesia.
- SUMM It has now been found that a **tramadol** material which includes various forms of **tramadol** as defined hereinafter can be combined with nonsteroidal antiinflammatory drugs (hereinafter NSAIDs) to produce analgesia. The combination employs lesser amounts of both the **tramadol** material and the NSAID than would be necessary to produce the same amount of analgesia if either was used alone. . . . of both drugs the side effects associated with each are reduced in number and degree. Surprisingly, the compositions comprising the **tramadol** material and one or more NSAIDs have been found to exhibit synergistic analgesic effects when combined in certain ratios. Particularly preferred compositions are those comprising a **tramadol** material and ibuprofen. The compositions according to this invention may also be useful in treating tussive conditions.
- DRWD FIG. 1 is an isobologram showing the analgesic effect of **tramadol** hydrochloride and ibuprofen composition on the acetylcholine-induced abdominal constriction in mice.
- DETD The present invention is generally directed to compositions comprising a **tramadol** material and an NSAID. The **tramadol** material

is any one of (1R, 2R or 1S, 2S)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol (**tramadol**), its N-oxide derivative ("**tramadol N-oxide**"), and its O-desmethyl derivative ("**O-desmethyl tramadol**") or mixtures thereof. It also includes the individual stereoisomers, mixtures of stereoisomers, including the racemates, pharmaceutically acceptable salts of the amines, such as the hydrochloride salt, solvates and polymorphs of the **tramadol** material. **Tramadol** is commercially available from Grunenthal or may be made by the process described in U.S. Pat. No. 3,652,589, which is.

- DETD **Tramadol N-oxide** is prepared by treating **tramadol** as a free base with an oxidizing agent, e.g., hydrogen peroxide (30%), in an organic solvent, e.g., methanol or isopropanol.
- DETD **O-desmethyl tramadol** is prepared by treating **tramadol** as a free base under O-demethylating reaction conditions, e.g., reacting it with a strong base such as NaH or KH.
- DETD . . . proquazone), phenylacetic acid derivatives such as diclofenac; etodolac and nabumetone. For the purposes of this invention, para-aminophenol derivatives such as **acetaminophen** are not considered NSAIDs because of their general lack of antiinflammatory activity. All of the NSAIDs are commercially available materials.
- DETD The NSAID and the **tramadol** material are generally present in a weight ratio of **tramadol** material to NSAID from about 1:1 to 1:200. Certain ratios result in a composition which exhibits synergistic analgesic effects. For example, in a composition comprising a **tramadol** material and an NSAID, the ratio of the **tramadol** material: NSAID is preferably from about 1:1 to 1:200; and, more preferably, from about 1:2 to 1:200. The most preferred ratios are from about 1:2 to 1:20. Compositions of a **tramadol** material and an NSAID within these weight ratios have been shown to exhibit synergistic analgesic effects.
- DETD A particularly preferred composition according to the present invention is a **tramadol** material and ibuprofen. The ratio of the **tramadol** material to ibuprofen in this preferred combination is from about 1:1 to 1:200, more preferably from about 1:2 to 1:200.
- DETD The **tramadol**/NSAID formulations according to the present invention may also contain therapeutically effective amounts of one or more other pharmaceutical actives including. . . pharmaceutically acceptable salts thereof) and combinations of any of the aforesaid pharmaceuticals. The aforesaid pharmaceuticals may be combined with a **tramadol/acetaminophen** formulation for the treatment of such ailments as allergies, sleep disorders, cough, colds, cold-like and/or flu symptoms in mammals including.
- DETD Pharmaceutical compositions comprising the **tramadol** material and the NSAID and when desired other pharmaceutical actives in an intimate admixture with a pharmaceutical carrier can be. . . it will be appreciated that the precise dose of the active ingredients will vary depending upon the particular NSAID and **tramadol** material being used. In the case wherein one or more other pharmaceutical components are added to the **tramadol**/NSAID composition those components may be added in therapeutically effective amounts known in the art and may be given at dosages.
- DETD Preparation of the Combined Doses of **Tramadol** and Ibuprofen
- DETD The preparation of different ratios of a **tramadol**/ibuprofen combination was effected by preparing solutions having concentrations expressed in mg.sub.drugs per 10 mL of distilled water. For example, 40 mg of **tramadol** as the free base and 40 mg of ibuprofen as the free base were added to 10 mL of water. . . 2 drops of TWEEN 80, a pharmacological dispersant, manufactured by Fisher Scientific Company, to yield the highest concentration of the **tramadol**/ibuprofen 1:1 (40mg:40mg) ratio. Each concentration of the ratio was prepared separately in a similar manner and injected in a volume of 10 mL/kg per

mouse. Similarly, the other ratios of **tramadol**/ibuprofen listed in Table 1 were prepared at the various concentrations.

DETD Preparation of the Combined Doses of **Tramadol** N-oxide and Ibuprofen

DETD First, **tramadol** N-oxide was prepared as set forth hereinafter. **Tramadol** hydrochloride (0.5 mol) was converted to its free base in basified water (pH>9) and then extracted with ether. The ether was evaporated to yield the crystalline hydrate of **tramadol**. The solid was then heated with steam under a high vacuum to remove as much water as possible to yield. . . . The solid was collected by filtration, washed with ethyl acetate and dried in vacuo to yield 126.6 g of the **tramadol** N-oxide (mp. 159.5°-160° C.).

DETD The preparation of different ratios of a **tramadol** N-oxide/ibuprofen combination is effected by preparing solutions having concentrations expressed in mg.sub.drugs per 10 mL of distilled water. For example, 40 mg of **tramadol** as the free base and 40 mg of ibuprofen as the free base is added to 10 mL of water. . . . 2 drops of TWEEN 80, a pharmacological dispersant, manufactured by Fisher Scientific Company, to yield the highest concentration of the **tramadol** N-oxide/ibuprofen 1:1 (40mg:40mg) ratio. Each concentration of the ratio is prepared separately in a similar manner.

DETD (-) and (+) Enantiomers of O-Desmethyl **Tramadol**: Their Syntheses and the Preparation of Doses of O-Desmethyl **Tramadol** with Ibuprofen

DETD First, O-desmethyl **tramadol** was prepared as set forth hereinafter. Diethylene glycol (125 mL) was added with cooling to potassium hydride (9.5 g) with. . . . maintained at <50° C. To the solution was added thiophenol (10 mL) dissolved in diethylene glycol (25 mL), and then (-)-**tramadol** as the free base (9.3 g) in diethylene glycol (50 mL) was added. The final reaction mixture was heated slowly. . . . was recrystallized from ethanol/ethyl ether and dried to yield 1.80 g of the salt of the (-) enantiomer of O-desmethyl **tramadol** (mp. 242°-3° C.), $[\alpha]_{\text{sub.D. sup.25}} = -32.9$ (C=1, EtOH).

DETD To prepare the (+) enantiomer of the title compound, the reaction was run under the same conditions except that (+)-**tramadol** as the free base was used instead of the (-)-**tramadol** to yield 2.8 g of the (+) enantiomer of O-desmethyl **tramadol** (mp. 242°-3° C.) $[\alpha]_{\text{sub.D. sup.25}} = +32.2$ (C=1, EtOH).

DETD . . . drops of TWEEN 80, a pharmacological dispersant, manufactured by Fisher Scientific Company, to yield the highest concentration of the O-desmethyl **tramadol**/ibuprofen 1:1 (40mg:40mg) ratio. Each concentration of the ratio is prepared separately in a similar manner and injected in a volume. . . .

DETD . . . utilized in determining the analgesic effects associated with the compositions of the invention. The mice were all dosed orally with **tramadol** hydrochloride (calculated as the base), which was completely dissolved in distilled water, and ibuprofen (calculated as the base), which was. . . .

DETD Mice, incubated with various doses of **tramadol** hydrochloride alone, ibuprofen alone, combined doses of **tramadol** hydrochloride and ibuprofen, or vehicle such as distilled water, or distilled water containing 2% by volume of Tween 80, were. . . . abdominal constriction response beginning immediately after receiving the acetylcholine dose, which was 30 minutes after receiving the oral administration of **tramadol** hydrochloride, ibuprofen, combined doses of **tramadol** hydrochloride and ibuprofen, or vehicle. Each mouse was used only once.

DETD . . . for the two drugs under additivity. ED50.sub.mix was then compared to ED50.sub.add via a Student's t-test. The ED50 value for **tramadol** hydrochloride alone was 5.5(4.8-6.4) mg/kg. The ED50 value for ibuprofen alone was 33.5 (24.1-46.5) mg/kg.

DETD The interaction between **tramadol** and ibuprofen was determined

at precise dosage ratios of **tramadol** hydrochloride and ibuprofen. Multiple (typically 4-6) coded doses of each selected combination were studied for analgesic effectiveness after 30 minutes.

DETD The interaction of **tramadol** hydrochloride and ibuprofen on the acetylcholine-induced abdominal constriction in mice was demonstrated by the data in Table I and is. . . i.e., unexpected enhancement of effects. The diagonal dashed lines radiating from the origin represent the dose ratios of ibuprofen to **tramadol** hydrochloride used in mice receiving the combined drug dosages. The bars through the ED50 points for the **tramadol** and ibuprofen composition represent the 95% confidence intervals of the ED50 value. The experimental data as represented in FIG. I establish that compositions having a ratio of **tramadol** to ibuprofen from about 1:1 to 1:200 (represented by the curved line) give unexpectedly enhanced activity since ED50.sub.mix is less. . .

DETD It is expected that based on these results, other NSAIDs, and particularly the propionic acid derivatives, when combined with a **tramadol** material, will produce similar synergistic results.

DETD TABLE I

TRAMADOL:IBUPROFEN

DRUG COMBINATIONS

DOSE (mg/kg, p.o.)

ED.sub.50 at 30 min (95% Cl's)

(**Tramadol**:**Ibuprofen**)

Tramadol

Ibuprofen

analgesia

Tramadol

Ibuprofen

tramadol only	2	0	3/15	5.5	--
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3	0	4/15	(4.8-6.4)	
---	---	------	-----------	--

4	0	14/45		
---	---	-------	--	--

6	0	20/45		
---	---	-------	--	--

8	0	40/60		
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10.				
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CLM What is claimed is:

1. A pharmaceutical composition comprising a **tramadol** material and ibuprofen, wherein the ratio of the **tramadol** material to the ibuprofen is a weight ratio of from about 1:1 to about 1:200.

2. The pharmaceutical composition of claim 1 wherein the **tramadol** material is tramado hydrochloride.

3. The pharmaceutical composition of claim 1 wherein the **tramadol** hydrochloride is racemic.

6. The pharmaceutical composition of claim 1, wherein the **tramadol** material is **tramadol** hydrochloride.

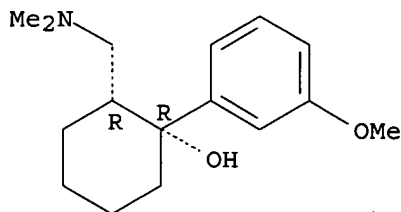
. . . comprising administering to the mammal an effective amount of a pharmaceutical composition for treating pain and tussive conditions comprising a **tramadol** material and ibuprofen, wherein the ratio of the **tramadol** material to the ibuprofen is a weight ratio of from about 1:1 to about 1:200.

. . . in a mammal comprising administering to the mammal an effective amount of a pharmaceutical composition for treating pain comprising a **tramadol** material and ibuprofen, wherein the ratio of the **tramadol** material to the ibuprofen is a weight ratio of from about 1:1 to about 1:200.

15. The method of claim 14, wherein the **tramadol** material is **tramadol** hydrochloride.

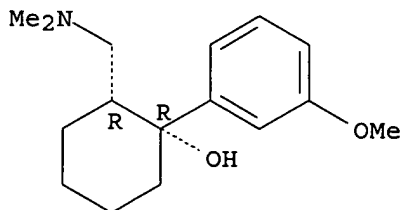
- IT 53-86-1D, Indomethacin, mixts. with tramadol derivative 5104-49-4D, Flurbiprofen, mixts. with tramadol derivative 15687-27-1D, Ibuprofen, mixts. with tramadol derivative 21256-18-8D, Oxaprozin, mixts. with tramadol derivative 22071-15-4D, Ketoprofen, mixts. with tramadol derivative 22204-53-1D, Naproxen, mixts. with tramadol derivative 27203-92-5D, Tramadol, mixts. with anti-inflammatory agent (analgesic compns. containing, synergistic)
- IT 34597-40-5D, Fenoprofen calcium, mixts. with tramadol derivative 36282-47-0D, Tramadol hydrochloride, mixts. with anti-inflammatory agent 38194-50-2D, Sulindac, mixts. with tramadol derivative 154605-61-5 (analgesic compns. containing, synergistic)
- IT 27203-92-5, Tramadol (oxidation of)
- IT 144830-14-8P, (+)-O-Desmethyltramadol 144830-15-9P, (-)-O-Desmethyltramadol 147441-56-3P, Tramadol N-oxide (preparation of and synergic analgesic composition containing inflammation inhibitors and)
- IT 27203-92-5D, Tramadol, mixts. with anti-inflammatory agent 36282-47-0D, Tramadol hydrochloride, mixts. with anti-inflammatory agent (analgesic compns. containing, synergistic)
- RN 27203-92-5 USPATFULL
- CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



- RN 36282-47-0 USPATFULL
- CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



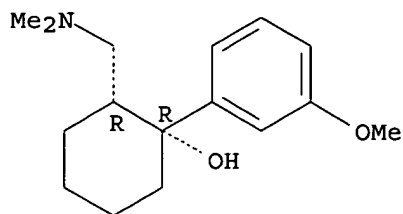
IT 27203-92-5, Tramadol

(oxidation of)

RN 27203-92-5 USPATFULL

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel-
(9CI) (CA INDEX NAME)

Relative stereochemistry.



IT 144830-14-8P, (+)-O-Desmethyltramadol 144830-15-9P,

(-)-O-Desmethyltramadol 147441-56-3P, Tramadol N-oxide

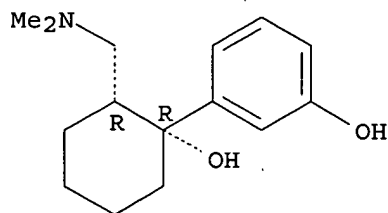
(preparation of and synergic analgesic composition containing inflammation
inhibitors

and)

RN 144830-14-8 USPATFULL

CN Phenol, 3-[(1R,2R)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]- (9CI)
(CA INDEX NAME)

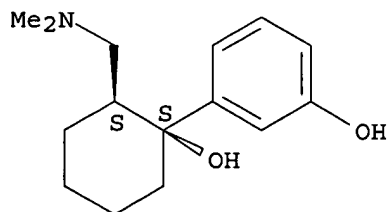
Absolute stereochemistry. Rotation (+).



RN 144830-15-9 USPATFULL

CN Phenol, 3-[(1S,2S)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]- (9CI)
(CA INDEX NAME)

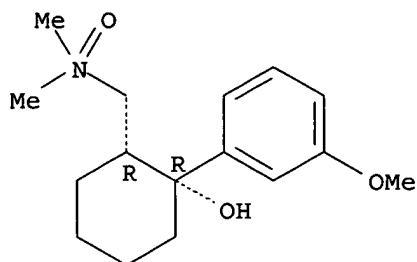
Absolute stereochemistry. Rotation (-).



RN 147441-56-3 USPATFULL

CN Cyclohexanol, 2-[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)-,
(1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L117 ANSWER 4 OF 10 USPATFULL on STN

AN 95:103506 USPATFULL

TI Composition comprising a **tramadol** material and any of codeine, oxycodone or hydrocodone and their use

IN **Raffa, Robert B.**, Norristown, PA, United States

Vaught, Jeffrey L., Perkasie, PA, United States

PA McNeil Lab, Inc., Spring House, PA, United States (U.S. corporation)

PI US 5468744 19951121

AI US 1994-268382 19940630 (8)

RLI Continuation of Ser. No. US 1992-976728, filed on 16 Nov 1992, now abandoned which is a continuation of Ser. No. US 1991-755923, filed on 6 Sep 1991, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Henley, III, Raymond; Assistant Examiner: Jarvis, William R. A.

LREP Palo, Ralph R.

CLMN Number of Claims: 12

ECL Exemplary Claim: 1

DRWN 2 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 504

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to compositions comprising a **tramadol** material selected from the group consisting of **tramadol**, its stereoisomers and its pharmaceutically acceptable salts and either codeine or oxycodone, and their use in treating pain. When the components, i.e., **tramadol** materials and either of codeine or oxycodone, of the composition are within certain ratios of pharmacological effects of the compositions are superadditive (synergistic).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Composition comprising a **tramadol** material and any of codeine, oxycodone or hydrocodone and their use

IN **Raffa, Robert B.**, Norristown, PA, United States

IN **Vaught, Jeffrey L.**, Perkasie, PA, United States

AB This invention relates to compositions comprising a **tramadol** material selected from the group consisting of **tramadol**, its stereoisomers and its pharmaceutically acceptable salts and either codeine or oxycodone, and their use in treating pain. When the components, i.e., **tramadol** materials and either of codeine or oxycodone, of the composition are within certain ratios of pharmacological effects of the compositions.

SUMM . . . a class of analgesic cycloalkanol-substituted phenol esters having a basic amine group in the cycloalkyl ring. The compound (1RS, 2RS) trans-2-[(dimethylamino)-methyl]-1-(3-methoxyphenyl)cyclohexanol, commonly known as **tramadol**, is specifically disclosed therein. A series of articles pertaining to the pharmacology, toxicology and clinical studies of **tramadol** are found in *Arzneim, Forsch*

(Drug Res.), 28(1), 114 (1978). Driessen et al., Arch. Pharmacol., 341, R104 (1990) disclose that **tramadol** produces its analgesic effect through a mechanism that is neither fully opioid-like nor non-opioid-like. The Abstracts of the VI th World Congress on Pain, Apr. 1-6 (1990) discloses that **tramadol** hydrochloride is an orally active pure agonist opioid analgesic. However, clinical experience indicates that **tramadol** lacks many of the typical-side effects of opioid agonists, e.g., respiratory depression (W. Vogel et al., *Arzneim, Forsch, (Drug Res.)*, . . . Yanagita, *Arzneim, Forsch. (Drug Res.)*, 28(1), 158 (1978)). When given at a dose of 50 mg by rapid i.v. injection, **tramadol** may however, produce certain side effects unique to **tramadol** including hot flushes and sweating. Despite theses side effects, **tramadol**'s combination of non-opioid and opioid activity makes **tramadol** a very unique drug. **Tramadol** is currently being marketed by Grunenthal GMBH in Germany as an analgesic.

- SUMM . . . al., Arch. Int. Pharmacodyn., 235, 116 (1978) report superadditive analgesia with a 1:125 mixture of butorphanol, another opioid analgesic, and **acetaminophen** (APAP), a non-opioid analgesic, whereas a 1:10 mixture did not show any statistically-significant superadditive analgesia.
- SUMM However, the prior art, does not suggest or disclose that **tramadol**, an "atypical" opioid analgesic, can or should be combined with another analgesic, particularly an opioid analgesic, to lessen the side. . . .
- SUMM It has now been found that a **tramadol** material which includes various forms of **tramadol** as defined hereinafter can be combined with certain opioids, codeine, oxycodone and hydrocodone, to produce an analgesic effect. Each of. . . structure; i.e., each one has a 3-methoxy substituent on the aromatic moiety. The combination employs lesser amounts of both the **tramadol** material and the opioid than would be necessary to produce the same amount of analgesia if either was used alone.. . . of both drugs the side effects associated with each are reduced in number and degree. Surprisingly, the compositions comprising a **tramadol** material and any of codeine, oxycodone or hydrocodone have been found to exhibit synergistic analgesic effects when combined in certain. . . .
- DRWD FIG. 1 is an isobologram showing the analgesic effect of **tramadol** hydrochloride and codeine phosphate compositions on tail-flick latency in mice; and
- DRWD FIG. 2 is an isobologram showing the analgesic effect of **tramadol** hydrochloride and oxycodone hydrochloride composition on tail-flick latency in mice.
- DETD The present invention is directed to compositions comprising a **tramadol** material and any one of codeine, oxycodone or hydrocodone and mixtures thereof.
- DETD The **tramadol** material according to the present invention is any one of (1R, 2R or 1S, 2S)-(dimethylaminomethyl)-1-(3-methoxyphenyl)-cyclohexanol (**tramadol**), its N-oxide derivative ("**tramadol** N-oxide"), and its O-desmethylated derivative ("**O-desmethyl tramadol**") or mixtures thereof. It also includes the individual stereoisomers, mixtures of stereoisomers including the racemates, pharmaceutically acceptable salts of the amines, such as the hydrochloride salt, solvates and polymorphs thereof. **Tramadol** is commercially available from Grunenthal or may be made by the process described in U.S. Pat. No. 3,652,589, which is. . . .
- DETD **Tramadol** N-oxide is prepared by treating **tramadol** as a free base with an oxidizing agent, e.g., hydrogen peroxide (30%), in an organic solvent, e.g., methanol or isopropanol,. . . .
- DETD O-Desmethyl **tramadol** is prepared by treating **tramadol** as a free base under O-desmethylating reaction conditions, e.g., reacting it with a strong base such as NaH or KH,. . . .
- DETD The **tramadol** material and the opioid material are generally

present in a weight ratio of **tramadol** material to opioid material of from about 200:1 to 1:20. This ratio varies within the disclosed range depending upon the. . . ratios within this range will result in a composition which exhibits synergistic analgesic effects. For example, in a composition comprising **tramadol** and codeine the ratio of the components is from about 20:1 to 1:20, preferably from about 2:1 to 1:2, and, more preferably, from about 2:1 to 1:1. In a composition comprising **tramadol** and oxycodone, the ratio of the components is from about 200:1 to 1:1; more preferably from about 20:1 to about. . .

- DETD Pharmaceutical compositions comprising the **tramadol** material and any of codeine, oxycodone or hydrocodone as the active ingredients in intimate admixture with a pharmaceutical carrier can. . .
- DETD Preparation of the Combined Doses of **Tramadol** and Codeine
- DETD . . . having a concentration expressed in mg.sub.drug(s) per 5 mL of distilled water. For example, in the case of the 1:20 **tramadol** :codeine ratio, 9.1 mg of **tramadol** hydrochloride (=8.0 mg of **tramadol** as the base) and 217.1 mg of codeine phosphate (=160.0 mg of codeine as the free base) were each dissolved. . . combined to prepare the final desired drug combination per 10 mL of distilled water. For example, 5 mL of the **tramadol** stock solution was combined with 5 mL of the codeine stock solution to yield the 1:20 dose, (i.e., 8 mg **tramadol**:160 mg codeine) in 10 mL of water. Then 10 mL/kg of the stock solution was injected into the mouse. See, . . .
- DETD Preparation of the Combined Doses of **Tramadol** and Oxycodone
- DETD The preparation of different ratios of a **tramadol**/oxycodone combination is effected by preparing a stock solution having a concentration expressed in mg.sub.drugs per 10 mL of dissolved water. For example, 80 mg of **tramadol** as the free base and 4 mg of oxycodone as the free base are dissolved in 10 mL of water to yield the stock solution of (80 mg:4 mg) **tramadol**/oxycodone combination per 10 mL of water. The stock solution of the drug combination is then diluted with a sufficient amount. . . lower doses of the drug combination per 10 mL of dissolved water. For example, 5 mL of the stock 20:1 **tramadol**/oxycodone combination are diluted with an equal volume of distilled water to yield the lower 20:1 dose, i.e., (40 mg:2 mg), . . .
- DETD Preparation of the Combined Doses of **Tramadol** and Hydrocodone
- DETD The preparation of different ratios of a **tramadol**/hydrocodone combination is effected by preparing a stock solution having a concentration expressed in mg.sub.drugs per 10 mL of dissolved water. For example, 160 mg of **tramadol** as the free base and 160 mg of hydrocodone as the free base are dissolved in 10 mL of water to yield the stock solution of (160 mg:160 mg) **tramadol**/hydrocodone combination per 10 mL of water. The stock solution of the drug combination is then diluted with a sufficient amount. . . lower doses of the drug combination per 10 mL of dissolved water. For example, 5 mL of the stock 1:1 **tramadol**/hydrocodone combination are diluted with an equal volume of distilled water to yield the lower 1:1 dose, (i.e., 80 mg:80 mg). . .
- DETD **Tramadol** N-oxide: Its Synthesis and the Preparation of Doses of **Tramadol** N-oxide with an Opioid
- DETD First, **tramadol** N-oxide was prepared as set forth hereinafter. **Tramadol** hydrochloride (0.5 mol) was converted its free base in basified water (pH >9) and then extracted with ether. The ether was evaporated to yield the crystalline hydrate of **tramadol**. The solid was then heated with steam under a high vacuum to remove as much water as possible to yield. . . The solid was collected by filtration, washed with ethyl acetate and dried in vacuo to yield 126.6 g of the **tramadol** N-oxide (mp. 159.5°-160° C.).
- DETD The preparation of different ratios of a **tramadol** N-oxide/opioid combination is effected by preparing a stock solution that corresponds to the highest dose of a particular ratio of the

tramadol N-oxide/opioid combination having a concentration expressed in mg.sub.drugs per 10 mL of distilled water. For example, 160 mg of **tramadol** N-oxide as the free base and 160 mg of the opiate oxycodone as the free base are dissolved in 10 mL of distilled water to yield the highest dose of the 1:1 (160 mg:160 mg)

tramadol N-oxide/oxycodone combination per 10 mL of water. The stock solution of the drug combination is then diluted with a sufficient. . . lower doses of the drug combination per 10 mL of dissolved water. For example, 5 mL of the stock 1:1 **tramadol** N-oxide/oxycodone combination are diluted with an equal volume of distilled water to yield the lower 1:1 dose (i.e., 80 mg:80. . .

DETD (-) and (+) Enantiomers of O-Desmethyl **Tramadol**: Their Syntheses and the Preparation of Doses of O-Desmethyl **Tramadol** with an Opioid

DETD First, O-desmethyl **tramadol** was prepared as set forth hereinafter. Diethylene glycol (125 mL) was added with cooling to potassium hydride (9.5 g) with. . . maintained at <50° C. To the solution was added thiophenol (10 mL) dissolved in diethylene glycol (25 mL), and then (-)-**tramadol** as the free base (9.3 g) in diethylene glycol (50 mL) was added. The final reaction mixture was heated slowly. . . was recrystallized from ethanol/ethyl ether and dried to yield 1.80 g of the salt of the (-) enantiomer of O-desmethylated **tramadol** (mp. 242°-3° C.),
[α].sub.D.sup.25 = -32.9 (C=1, EtOH).

DETD To prepare the (+) enantiomer of the title compound, the reaction was run under the same conditions except that (+)-**tramadol** as the free base was used instead of the (-)-**tramadol** to yield 2.8 g of the (+) enantiomer of O-desmethyl **tramadol** (mp. 242°-3° C.) [α].sub.D.sup.25 = +32.2 (C=1, EtOH).

DETD The preparation of different ratios of O-desmethyl **tramadol** /opioid combinations is effected by preparing a stock solution that corresponds to the highest dose of a particular ratio of the O-desmethyl **tramadol**/opioid combination having a concentration expressed in mg.sub.drugs per 10 mL of distilled water. For example, 160 mg of O-desmethyl **tramadol** as the free base and 80 mg of the opiate hydrocodone as the free base are dissolved in 10 mL of distilled water to yield the highest dose of a 2:1 (160 mg:80 mg) O-desmethyl **tramadol**/hydrocodone combination per 10 mL of water. The stock solution of the drug combination is then diluted with a sufficient amount. . . lower doses of the drug combination per 10 mL of distilled water. For example, 5 mL of the stock 2:1 **tramadol** O-desmethyl/hydrocodone combination are diluted with an equal volume of distilled water to yield a lower 2:1 dose (i.e., 80 mg:40. . .

DETD . . . two drugs under additivity. ED50.sub.mix was then compared to ED50.sub.add via a t-test. The ED50 value (95% confidence interval) for **tramadol** hydrochloride alone was 76.8 (59.2-99.7) mg/kg. The ED50 value (and 95% confidence interval) for codeine phosphate alone was 71.3 (52.0-97.7). . .

DETD The interaction between **tramadol** and codeine or hydrocodone were determined at precise dosage ratios of **tramadol** hydrochloride and codeine or oxycodone. Multiple (typically 4-6) coded doses of each selected combination were studied for analgesic effectiveness after. . .

DETD The interaction of **tramadol** hydrochloride and codeine phosphate or oxycodone sulfate on tail-flick latency in mice was demonstrated by the data in Tables I. . . indicate superadditivity, i.e., unexpected enhancement of effects. The diagonal dashed lines radiating from the origin represent the dose ratios of **tramadol** hydrochloride to codeine phosphate (FIG. 1) or oxycodone sulfate (FIG. 2) used in mice receiving the combined drug dosages. The bars through the ED50 points for **tramadol** and codeine or oxycodone compositions represent the 95% confidence intervals of the ED50.

DETD The experimental data as represented in FIG. I establishes that

compositions having a ratio of **tramadol** to codeine from 1:20 to 20:1 (represented by the curved line) give unexpectedly enhanced activity since ED₅₀.sub.mix is less than ED₅₀.sub.add. The experimental data as represented in FIG. II similarly establishes that compositions having a ratio of **tramadol** to oxycodone from 200:1 to 1:1 also give unexpectedly enhanced activity. Furthermore, the use of hydrocodone in a composition of. . .

DETD

TABLE I

TRAMADOL:CODEINE				
DRUG COMBINATION				
DOSE (mg/kg, p.o.)			ED.sub.50 at 15 min (95% Cl's)	
(Tramadol:Codeine)				
Tramadol				
Codeine				
Analgesia				
			Tramadol	
			Codeine	
<hr/>				
tramadol only				
	20	0	0/10	
	40	0	1/10	
	80	0	4/10	76.8 --
	160	0	9/10	(59.2-99.7)
	200	0	10/10	
20:1	20.	.	.	
DETD				
TABLE II				

TABLE II

TRAMADOL:OXYCODONE				
DRUG COMBINATION				
DOSE (mg/kg, p.o.)			ED.sub.50 at 15 min (95% Cl's)	
(Tramadol:Codeine)				
Tramadol				
Codeine				
Analgesia				
			Tramadol	
			Oxycodone	
<hr/>				
tramadol only				
	20	0	0/10	
	40	0	2/10	
	80	0	4/10	76.8 --
	160	0	9/10	(59.2-99.7)
	200	0	10/10	
200:1	20.	.	.	

CLM

What is claimed is:

1. A pharmaceutical composition comprising a **tramadol** material selected from the group consisting of **tramadol**, its stereoisomers and its pharmaceutically acceptable salts and an opioid selected from the group consisting of codeine and oxycodone, wherein the weight ratio of the **tramadol** material to the opioid is of from about 1:20 to about 20:1.

3. The pharmaceutical composition of claim 2 wherein the **tramadol** material is **tramadol** hydrochloride.

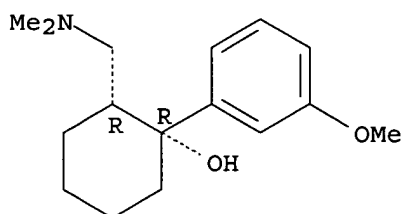
4. The pharmaceutical composition of claim 3 wherein the **tramadol** hydrochloride is racemic.

8. The pharmaceutical composition of claim 7 wherein said **tramadol** material is **tramadol** hydrochloride.

9. The pharmaceutical composition of claim 8 wherein the tramadol hydrochloride is racemic.

- IT 36282-47-0, Tramadol hydrochloride
(conversion of, to hydrate)
IT 27203-92-5
(oxidation of)
IT 144830-14-8P, (+)-O-Desmethyltramadol 147441-56-3P,
Tramadol N-oxide 148218-19-3P, (-)-O-Desmethyltramadol
hydrochloride
(preparation of, analgesic compns. containing)
IT 36282-47-0, Tramadol hydrochloride
(conversion of, to hydrate)
RN 36282-47-0 USPATFULL
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-,
hydrochloride, (1R,2R)-rel- (9CI) (CA INDEX NAME)

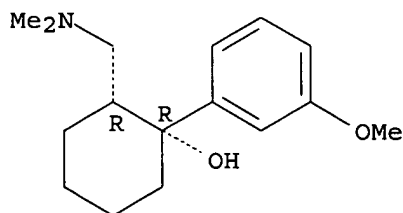
Relative stereochemistry.



● HCl

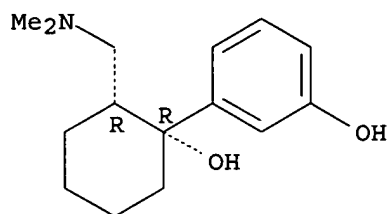
- IT 27203-92-5
(oxidation of)
RN 27203-92-5 USPATFULL
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel-
(9CI) (CA INDEX NAME)

Relative stereochemistry.



- IT 144830-14-8P, (+)-O-Desmethyltramadol 147441-56-3P,
Tramadol N-oxide 148218-19-3P, (-)-O-Desmethyltramadol
hydrochloride
(preparation of, analgesic compns. containing)
RN 144830-14-8 USPATFULL
CN Phenol, 3-[(1R,2R)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]- (9CI)
(CA INDEX NAME)

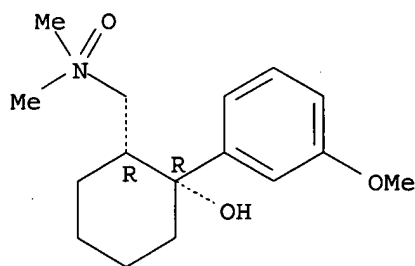
Absolute stereochemistry. Rotation (+).



RN 147441-56-3 USPATFULL

CN Cyclohexanol, 2-[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)-,
(1R,2R)-rel- (9CI) (CA INDEX NAME)

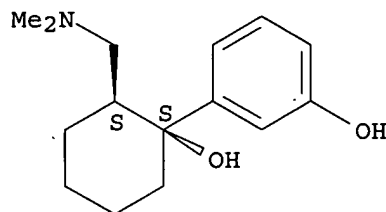
Relative stereochemistry.



RN 148218-19-3 USPATFULL

CN Phenol, 3-[(1S,2S)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-,
hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● HCl

L117 ANSWER 5 OF 10 USPATFULL on STN

AN 94:68779 USPATFULL

TI Composition comprising a **tramadol** material and
acetaminophen and its use

IN **Raffa, Robert B.**, Norristown, PA, United States
Vaught, Jeffrey L., Perkosie, PA, United States

PA McNeilab, Inc., Spring House, PA, United States (U.S. corporation)

PI US 5336691 19940809

AI US 1992-974865 19921110 (7)

RLI Continuation-in-part of Ser. No. US 1991-755924, filed on 6 Sep 1991,
now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Waddell, Frederick E.; Assistant Examiner: Jarvis,

William R. A.
LREP Palo, Ralph R.
CLMN Number of Claims: 15
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 555

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to a composition comprising a **tramadol** material and **acetaminophen**, and its use. As used herein **tramadol** refers to various forms of **tramadol**. The compositions are pharmacologically useful in treating pain and tussive conditions. The compositions are also subject to less opioid side-effects such as abuse liability, tolerance, constipation and respiratory depression. Furthermore, where the components of the compositions are within certain ratios the pharmacological effects of the compositions are superadditive (synergistic).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Composition comprising a **tramadol** material and **acetaminophen** and its use

IN **Raffa, Robert B.**, Norristown, PA, United States

IN **Vaught, Jeffrey L.**, Perkosie, PA, United States

AB This invention relates to a composition comprising a **tramadol** material and **acetaminophen**, and its use. As used herein **tramadol** refers to various forms of **tramadol**. The compositions are pharmacologically useful in treating pain and tussive conditions. The compositions are also subject to less opioid side-effects.

SUMM . . . analgesic cycloalkanol-substituted phenol esters having a basic amine group in the cycloalkyl ring. The compound (1RS, 2RS)-[(dimethylamino)-methyl]-1-(3-methoxyphenyl)cyclohexanol, commonly known as **tramadol**, is specifically disclosed therein. A series of articles pertaining to the pharmacology, toxicology and clinical studies of **tramadol** are found in *Arzneim. Forsch.* (Drug Res.), 28(I), 114 (1978). *Driessen et al.*, *Arch. Pharmacol.*, 341, R104 (1990) disclose that **tramadol** produces its analgesic effect through a mechanism that is neither fully opioid-like nor non-opioid-like. The Abstracts of the VI th World Congress on Pain, Apr. 1-6 (1990), disclose that **tramadol** hydrochloride is an orally active pure agonist opioid analgesic. However, clinical experience indicates that **tramadol** lacks many of the typical side effects of opioid agonists, e.g., respiratory depression (*W. Vogel et al.*, *Arzneim. Forsch.* (Drug Res.), 28(I), 158 (1978)). When given at a dose of 50 mg by rapid i.v. injection, **tramadol** may produce certain side effects unique to **tramadol** including hot flushes and sweating. Despite these side effects, **tramadol**'s combination of non-opioid and opioid activity makes **tramadol** a very unique drug. **Tramadol** is currently being marketed by Grunenthal GMBH as an analgesic.

SUMM As alternatives to using opioids, non-opioids such as **acetaminophen** (APAP) and aspirin are used as analgesics. APAP, like aspirin, is not subject to the tolerance, addiction and toxicity of.

SUMM . . . *al.*, *Arch. Int. Pharmacodyn.*, 235, 116 (1978) report superadditive analgesia with a 1:125 mixture of butorphanol, another opioid analgesic, and **acetaminophen** (APAP), a non-opioid analgesic, whereas a 1:10 mixture did not show any statistically significant superadditive analgesia.

SUMM The prior art, however, does not disclose that **tramadol** an `atypical` opioid analgesic, can or should be combined with another analgesic to lessen the side effects of each or to yield a composition comprising a **tramadol** material and another analgesic that exhibits superadditive analgesia.

SUMM It has now been found that a **tramadol** material which includes various forms of **tramadol** as defined hereinafter can be combined with APAP to produce analgesia. The combination employs lesser amounts of both the **tramadol** material and APAP than would be necessary to produce the same amount of analgesia if either was used alone. By . . . of both drugs the side effects associated with each are reduced in number and degree. Surprisingly, the compositions comprising the **tramadol** material and APAP have been found to exhibit synergistic analgesic effects when combined in certain ratios. The compositions according to. . .

DRWD FIG. 1 is an isobologram showing the analgesic effect of **tramadol** hydrochloride and **acetaminophen** composition on the acetylcholine-induced abdominal constriction in mice.

DETD The present invention is directed to compositions comprising a **tramadol** material and **acetaminophen**. The **tramadol** material is any one of (1R, 2R or 1S, 2S)-(dimethylaminomethyl)-1-(3-methoxyphenyl)-cyclohexanol (**tramadol**), its N-oxide derivative ("**tramadol** N-oxide"), and its O-desmethyl derivative ("O-desmethyl **tramadol**") or mixtures thereof. It also includes the individual stereoisomers, mixtures of stereoisomers, including the racemates, pharmaceutically acceptable salts of the amines, such as the hydrochloride salt, solvates and polymorphs of the **tramadol** material. **Tramadol** is commercially available from Grunenthal or may be made by the process described in U.S. Pat. No. 3,652,589, which is. . .

DETD **Tramadol** N-oxide is prepared by treating **tramadol** as a free base with an oxidizing agent, e.g., hydrogen peroxide (30%), in an organic solvent, e.g., methanol or isopropanol,. . .

DETD O-Desmethyl **tramadol** is prepared by treating **tramadol** as a free base under O-desmethylating reaction conditions, e.g., reacting it with a strong base such as NaH or KH,. . .

DETD The pharmacology of **acetaminophen** is reviewed by B. Ameer et al., Ann. Int. Med., 87, 202 (1977), and the preparation of **acetaminophen** is disclosed in U.S. Pat. No. 2,998,450, which is incorporated herein by reference.

DETD The APAP and the **tramadol** material are generally present in a weight ratio of **tramadol** material to APAP from about 1:1 to 1:1600. Certain ratios result in a composition which exhibits synergistic analgesic effects. For example, in a composition comprising a **tramadol** material and APAP, the ratio of the **tramadol** material: APAP is preferably from about 1:5 to 1:1600; and, more preferably, from about 1:19 to 1:800.

DETD The most preferred ratios are from about 1:19 to 1:50. Compositions of a **tramadol** material and APAP within these weight ratios have been shown to exhibit synergistic analgesic effects. In addition, the particular compositions. . .

DETD The **tramadol**/APAP formulations according to the present invention may also contain therapeutically effective amounts of one or more other pharmaceutical actives including. . . pharmaceutically acceptable salts thereof) and combinations of any of the aforesaid pharmaceuticals. The aforesaid pharmaceuticals may be combined with a **tramadol**/acetaminophen formulation for the treatment of such ailments as allergies, sleep disorders, cough, colds, cold-like and/or flu symptoms in mammals including. . .

DETD Pharmaceutical compositions comprising the **tramadol** material and **acetaminophen** and when desired other pharmaceutical actives in an intimate admixture with a pharmaceutical carrier can be prepared according to conventional. . . amounts of active components being used. In the case wherein one or more other pharmaceutical components are added to the **tramadol**/APAP composition those components may be added in amounts known in the art and may be given at dosages conventional for. . .

DETD Preparation of the Combined Doses of **Tramadol** and APAP

- DETD The preparation of different ratios of a **tramadol**/APAP combination is effected by first preparing a stock solution of **tramadol** having a concentration expressed in mg.sub.drugs per 10 mL of distilled water. For example, 8 mg of **tramadol** as the free base is dissolved per 10 mL of water to yield the highest dose of **tramadol** stock solution. The stock solution of the **tramadol** is then diluted with a sufficient amount of distilled water to prepare the lower doses of the **tramadol** per 10 mL of distilled water. The combinations are then made by adding 10 mL of each dilution to the appropriate mg of APAP to achieve the desired ratio of **tramadol** to APAP. For the 1:50 example: 400 mg of APAP as the free base is suspended with 10 mL of the 8 mg **tramadol** solution and 2 drops of TWEEN 80, a pharmacological dispersant, manufactured by Fisher Scientific Company, to yield the 1:50 ratio, . . .
- DETD Preparation of the Combined Doses of **Tramadol** N-oxide and APAP
- DETD First, **tramadol** N-oxide was prepared as set forth hereinafter. **Tramadol** hydrochloride (0.5 mol) was converted to its free base in basified water (pH >9) and then extracted with ether. The ether was evaporated to yield the crystalline hydrate of **tramadol**. The solid was then heated with steam under a high vacuum to remove as much water as possible to yield. . . . The solid was collected by filtration, washed with ethyl acetate and dried in vacuo to yield 126.6 g of the **tramadol** N-oxide (mp. 159.5°-160° C.).
- DETD The preparation of different ratios of a **tramadol** N-oxide/APAP combination is effected by first preparing a stock solution of **tramadol**-N-oxide having a concentration expressed in mg.sub.drugs per 10 mL of distilled water. For example, 8 mg of **tramadol** N-oxide as the free base is dissolved per 10 mL of water to yield the highest dose of **tramadol** stock solution. The stock solution of the **tramadol**-N-oxide is then diluted with a sufficient amount of distilled water to prepare the lower doses of the **tramadol** N-oxide per 10 mL of distilled water. The combinations are then made by adding 10 mL of each dilution to the appropriate mg of APAP to achieve the desired ratio of **tramadol** N-oxide to APAP. For the 1:50 example: 400 mg of APAP as the free base is suspended with 10 mL of the 8 mg **tramadol** N-oxide solution and 2 drops of TWEEN 80, a pharmacological dispersant, manufactured by Fisher Scientific Company, to yield the 1:50. . . .
- DETD (-) and (+) Enantiomers of O-Desmethyl **Tramadol**: Their Syntheses and the Preparation of Doses of O-Desmethyl **Tramadol** -with APAP
- DETD First, O-desmethyl **tramadol** was prepared as set forth hereinafter. Diethylene glycol (125 mL) was added with cooling to potassium hydride (9.5 g) with the. . . maintained at <50° C. To the solution was added thiophenol (10 mL) dissolved in diethylene glycol (25 mL), and then (-)-**tramadol** as the free base (9.3 g) in diethylene glycol (50 mL) was added. The final reaction mixture was heated slowly. . . was recrystallized from ethanol/ethyl ether and dried to yield 1.80 g of the salt of the (-) enantiomer of O-desmethyl **tramadol** (mp. 242°-3° C.), $[\alpha]_{\text{sub.D. sup.25}} = -32.9$ (C=1, EtOH).
- DETD To prepare the (+) enantiomer of the title compound, the reaction was run under the same conditions except that (+)-**tramadol** as the free base was used instead of the (-)-**tramadol** to yield 2.8 g of the (+) enantiomer of O-desmethyl **tramadol** (mp. 242°-3° C.) $[\alpha]_{\text{sub.D. sup.25}} = +32.2$ (C=1, EtOH).
- DETD The preparation of different ratios of a O-desmethyl/APAP combination is effected by first preparing a stock solution of O-desmethyl **tramadol** having a concentration expressed in mg.sub.drugs per 10 mL of distilled water. For example, 8 mg of O-desmethyl **tramadol** as the free base is dissolved per 10 mL of water to yield the highest dose of O-desmethyl **tramadol** stock solution. The stock

solution of the O-desmethyl **tramadol** is then diluted with a sufficient amount of distilled water to prepare the lower doses of the O-desmethyl **tramadol** per 10 mL of distilled water. The combinations are then made by adding 10 mL of each dilution to the appropriate mg of APAP to achieve the desired ratio of O-desmethyl **tramadol** to APAP. For the 1:50 example: 400 mg of APAP as the free base is suspended with 10 mL of the 8 mg O-desmethyl **tramadol** solution and 2 drops of TWEEN 80, a pharmacological dispersant, manufactured by Fisher Scientific Company, to yield the 1:50 ratio, . . .

- DETD . . . utilized in determining the analgesic effects associated with the compositions of the invention. The mice were all dosed orally with **tramadol** hydrochloride (calculated as the base), which was completely dissolved in distilled water, and **acetaminophen** (calculated as the base), which was completely dissolved in distilled water or in distilled water containing 2% by volume of . . .
- DETD Mice, intubated with various doses of **tramadol** hydrochloride alone, **acetaminophen** alone, combined doses of **tramadol** hydrochloride and **acetaminophen**, or vehicle such as distilled water, or distilled water containing 2% by volume of Tween 80, were injected intraperitoneally with. . . abdominal constriction response beginning immediately after receiving the acetylcholine dose, which was 30 minutes after receiving the oral administration of **tramadol** hydrochloride, **acetaminophen**, combined doses of **tramadol** hydrochloride and **acetaminophen**, or vehicle. Each mouse was used only once.
- DETD . . . for the two drugs under additivity. ED₅₀.sub.mix was then compared to ED₅₀.sub.add via a Student's t-test. The ED₅₀ value for **tramadol** hydrochloride alone was 5.5(4.8-6.4) mg/kg. The ED₅₀ value for **acetaminophen** alone was 164.3 (122.7-219.9) mg/kg.
- DETD The interaction between **tramadol** and **acetaminophen** was determined at precise dosage ratios of **tramadol** hydrochloride and **acetaminophen**. Multiple (typically 4-6) coded doses of each selected combination were studied for analgesic effectiveness after 30 minutes using an experimental. . .
- DETD The interaction of **tramadol** hydrochloride and **acetaminophen** on the acetylcholine-induced abdominal constriction in mice was demonstrated by the data in Table I and is shown in the. . . i.e., unexpected enhancement of effects. The diagonal dashed lines radiating from the origin represent the dose ratios of APAP to **tramadol** hydrochloride used in mice receiving the combined drug dosages. The bars through the ED₅₀ points for the **tramadol** and APAP composition represent the 95% confidence intervals of the ED₅₀ value. The experimental data as represented in FIG. I establishes that compositions having a ratio of **tramadol** to APAP from 1:1 to 1:1600 (represented by the curved line) give unexpectedly enhanced activity since ED₅₀.sub.mix is less than. . .

DETD TABLE I

TRAMADOL:APAP		
DRUG COMBINATIONS		
DOSE (mg/kg, p.o.)		
ED.sub.50 30 min (95% CI's)		
(Tramadol:APAP)		
Tramadol	APAP	analgesia
Tramadol		APAP

tramadol only	2	0	3/15
	3	0	4/15
	4	0	14/45

6 0 20/45
 5.5
 8 0 40/60
 (4.8-6.4)
 10 0. . .

CLM What is claimed is:

1. A pharmaceutical composition comprising a **tramadol** material and **acetaminophen**, wherein the ratio of the **tramadol** material to **acetaminophen** is a weight ratio from about 1:1 to about 1:1600.

2. The pharmaceutical composition of claim 1 wherein the **tramadol** material is **tramadol** hydrochloride.

3. The pharmaceutical composition of claim 2 wherein the **tramadol** hydrochloride is racemic.

IT 144830-14-8P 144830-15-9P

(analgesic acetaminophen-tramadol compns.)

IT 103-90-2, Acetaminophen 27203-92-5, Tramadol
 36282-47-0, Tramadol hydrochloride 147441-56-3,
 Tramadol N-oxide

(analgesic acetaminophen-tramadol compns.)

IT 148229-78-1, (+)-Tramadol 148229-79-2, (-)-Tramadol
 (analgesic acetaminophen-tramadol compns.)

IT 148218-19-3P

(analgesic acetaminophen-tramadol compns.)

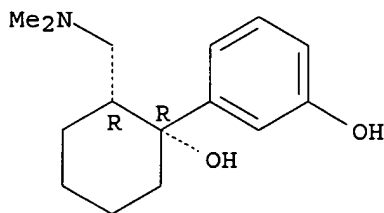
IT 144830-14-8P 144830-15-9P

(analgesic acetaminophen-tramadol compns.)

RN 144830-14-8 USPATFULL

CN Phenol, 3-[(1R,2R)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]- (9CI)
 (CA INDEX NAME)

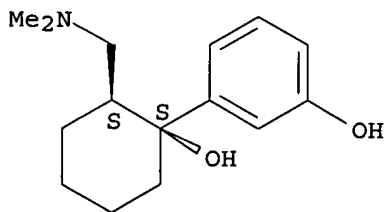
Absolute stereochemistry. Rotation (+).



RN 144830-15-9 USPATFULL

CN Phenol, 3-[(1S,2S)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]- (9CI)
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

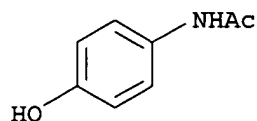


IT 103-90-2, Acetaminophen 27203-92-5, Tramadol
 36282-47-0, Tramadol hydrochloride 147441-56-3,

Tramadol N-oxide
(analgesic acetaminophen-tramadol compns.)

RN 103-90-2 USPATFULL

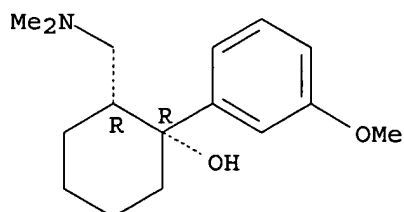
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



RN 27203-92-5 USPATFULL

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

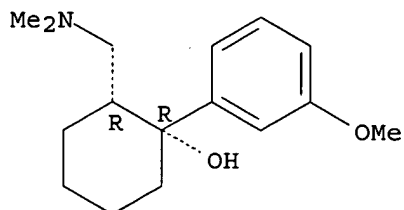
Relative stereochemistry.



RN 36282-47-0 USPATFULL

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

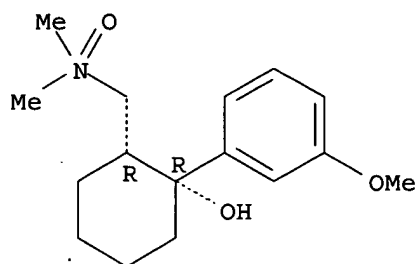


● HCl

RN 147441-56-3 USPATFULL

CN Cyclohexanol, 2-[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

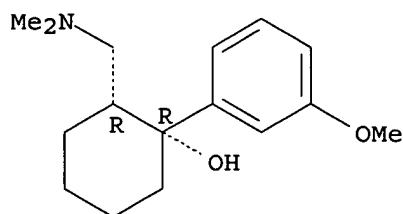


IT 148229-78-1, (+)-Tramadol 148229-79-2, (-)-Tramadol
(analgesic acetaminophen-tramadol compns.)

RN 148229-78-1 USPATFULL

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-,
hydrochloride, (1R,2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

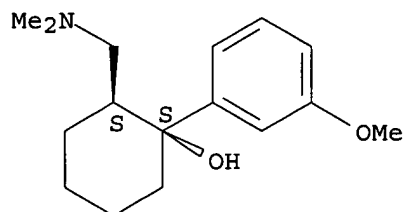


● HCl

RN 148229-79-2 USPATFULL

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-,
hydrochloride, (1S,2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● HCl

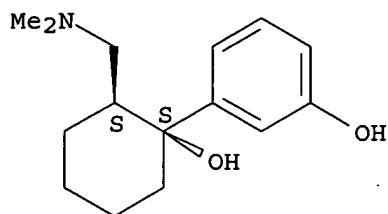
IT 148218-19-3P

(analgesic acetaminophen-tramadol compns.)

RN 148218-19-3 USPATFULL

CN Phenol, 3-[(1S,2S)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-,
hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● HCl

L117 ANSWER 6 OF 10 USPATFULL on STN

AN 93:52619 USPATFULL

TI **Tramadol** N-oxide material, enantiomers and compositions thereof, and their use

IN Maryanoff, Cynthia A., New Hope, PA, United States

Raffa, Robert B., Norristown, PA, United States

Villani, Frank J., Perkasie, PA, United States

PA McNeilab, Inc., Spring House, PA, United States (U.S. corporation)

PI US 5223541 19930629

AI US 1991-759259 19910913 (7)

DT Utility

FS Granted

EXNAM Primary Examiner: Raymond, Richard L.; Assistant Examiner: O'Sullivan, P.

LREP Palo, Ralph R.

CLMN Number of Claims: 7

ECL Exemplary Claim: 1

DRWN 2 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 249

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to a **tramadol** N-oxide material, enantiomers and compositions thereof and their use. The **tramadol** N-oxide material and compositions thereof are pharmacologically useful in treating pain, diarrhea and tussive conditions. The **tramadol** N-oxide is also subject to less side-effects as compared to pure opiate based compositions, such as abuse liability, tolerance, constipation and respiratory depression. Furthermore, the **tramadol** N-oxide material when administered orally exhibits analgesia for a longer duration than an equi-analgesic amount of **tramadol**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI **Tramadol** N-oxide material, enantiomers and compositions thereof, and their use

IN **Raffa, Robert B.**, Norristown, PA, United States

AB This invention relates to a **tramadol** N-oxide material, enantiomers and compositions thereof and their use. The **tramadol** N-oxide material and compositions thereof are pharmacologically useful in treating pain, diarrhea and tussive conditions. The **tramadol** N-oxide is also subject to less side-effects as compared to pure opiate based compositions, such as abuse liability, tolerance, constipation and respiratory depression. Furthermore, the **tramadol** N-oxide material when administered orally exhibits analgesia for a longer duration than an equi-analgesic amount of **tramadol**.

SUMM . . . discloses a class of analgesic cycloalkanol-substituted phenol esters having a basic amine group in the cycloalkyl ring. The compound (1RS, 2RS)-2-[(dimethylamino)-methyl]-1-(3-methoxyphenyl)cyclohexanol,

commonly known as **tramadol**, is specifically disclosed therein. A series of articles pertaining to the pharmacology, toxicology and clinical studies of **tramadol** are found in *Arzneim. Forsch. (Drug Res.)*, 28(I), 114 (1978). Driessen et al., *Arch. Pharmacol.*, 341, R104 (1990) disclose that **tramadol** produces its analgesic effect through a mechanism that is neither fully opioid-like nor non-opioid-like. The Abstracts of the Vith World Congress on Pain, Apr. 1-6 (1990) disclose that **tramadol** hydrochloride is an orally active pure opioid agonist analgesic. However, clinical experience indicates that **tramadol** lacks many of the typical side effects of opioid agonists, e.g., respiratory depression (W. Vogel et al., *Arzneim. Forsch. (Drug Res.)*, 28(I), 158 (1978)). When given at a dose of 50 mg by rapid I.V. injection, **tramadol** may, however, produce certain side effects unique to **tramadol** including hot flashes and sweating. Another disadvantage to the use of **tramadol** is that it is an immediate acting drug and thus must be taken a number of times over a 24 hour period to sustain analgesia. Despite these disadvantages, **tramadol**'s combination of non-opioid and opioid activity makes **tramadol** a very unique drug. **Tramadol** is currently being marketed by Grunenthal GMBH in Germany as an analgesic.

SUMM . . . assess the pharmacological activity of the derivatives. Flick et al., *Arzneim. Forsch.*, 28, 107 (1978), disclose that the only desmethyl **tramadol** that exhibits analgesia is the O-desmethyl **tramadol**, and the reference also discloses that the O-desmethyl **tramadol** is analgesically more effective than **tramadol**. B. Klentey et al., *Arzneim. Forsch.*, 7, 594 (1957) disclose that the N-oxides of dihydromorphinone, morphinone and dihydrohydroxycodone do not.

SUMM The prior art, therefore, does not disclose or suggest an N-oxide of a **tramadol** material or that the N-oxide of a **tramadol** material would exhibit an analgesic effect or would exhibit a pharmacological effect having a longer duration, e.g., of analgesia, than its corresponding non-N-oxide, e.g., **tramadol**.

SUMM Accordingly, the present invention is directed to a **tramadol** N-oxide material having the following formula I: ##STR1## enantiomers and compositions thereof and their use. The **tramadol** N-oxide material and compositions thereof are pharmacologically useful in treating pain, diarrhea and tussive conditions. The **tramadol** N-oxide material is also subject to less side-effects as compared to a pure opioid or opiate based compositions, such as abuse liability, tolerance, constipation and respiratory depression. Furthermore, **tramadol** N-oxide when administered orally exhibits analgesia for a longer duration than an equi-analgesic amount of **tramadol**. As defined herein longer duration means for more than 2 hours and preferably for 4 to up to at least.

DRWD FIG. 1 is a graph showing the % of analgesia effected versus the dose of **tramadol** and **tramadol** N-oxide ascertained by the abdominal constriction test in mice; and

DRWD FIG. 2 is a bar graph showing time course of the % of analgesia effected by **tramadol** N-oxide versus **tramadol** hydrochloride at equianalgesic doses ascertained by the abdominal constriction test in mice.

DETD More particularly, the **tramadol** N-oxide material according to the present invention is either of the N-oxide derivative of (1R, 2R or 1S, 2S)-2-(dimethylaminomethyl)-1-(3-methoxyphenyl)-cyclohexanol-N-oxide ("**tramadol** N-oxide") or mixtures thereof. It also includes the individual stereoisomers, such as those of formulas II & III: ##STR2## and.

DETD **Tramadol** N-oxide is prepared by treating **tramadol** (commercially available from Grunenthal or may be made by the process described in U.S. Pat. No. 3,652,589, which is herein.

DETD The **tramadol** N-oxide material may be used alone or be combined

with other active ingredients such as analgesic agents including acetaminophen, codeine, oxycodone, hydrocodone and ibuprofen. This ratio of the tramadol N-oxide material and the other active ingredient will vary depending upon the particular components of the composition.

DETD Pharmaceutical compositions comprising the tramadol N-oxide material alone or in combination with one or more other active ingredients in an intimate admixture with a pharmaceutical. . .

DETD Example 1: Tramadol N-oxide

DETD Tramadol N-oxide was prepared as set forth hereinafter. Tramadol hydrochloride (0.5 mol) was converted its free base in basified water (pH>9) and then extracted with ether. The solid was. . . The solid was collected by filtration, washed with ethyl acetate and dried in vacuo to yield 126.6 g of the tramadol N-oxide (mp. 159.5°-160° C.).

DETD . . . utilized in determining the analgesic effects associated with the compositions of the invention. The mice were all dosed orally with tramadol hydrochloride or tramadol N-oxide (calculated as the base),

DETD Mice, intubated with various doses of tramadol hydrochloride or tramadol N-oxide were injected intraperitoneally with a challenge dose of acetylcholine bromide. The acetylcholine was completely dissolved in distilled water; the. . . abdominal constriction response beginning immediately after receiving the acetylcholine dose, which was 30 minutes after receiving the oral administration of tramadol hydrochloride or tramadol N-oxide. Each mouse was used only once.

DETD . . . the dose of each compound which produced an equal level (90%) of analgesia (the ED90 dose). The ED90 dose of tramadol hydrochloride was estimated to be 12 mg/kg p.o. (See, FIG. 1) and the ED90 dose of tramadol N-oxide was estimated to be 40 mg/kg p.o. (See, FIG. 1). The respective ED90 doses of both compounds were then. . . of mice at various times prior to the challenge by acetylcholine as described above. Separate groups of mice received either tramadol or tramadol N-oxide at 15, 30, 60, 120, 180, 240 or 300 minutes prior to the acetylcholine challenge. The percentage of analgesia. . . response according to equation {1}. The duration of analgesic effect (determined as the time percentage analgesia dropped below 50%) of tramadol was between 60 and 120 minutes (See, FIG. 2), whereas the duration of analgesic effect for tramadol N-oxide was between 240 and 300 minutes. The greater duration of analgesic action of tramadol N-oxide at equi-analgesic doses to tramadol also demonstrates that for doses of equal duration, requiring raising the dose of tramadol, the level of tramadol required would be greater than the therapeutically prudent dose and, thus, would likely represent an unacceptable increase in the side effects, and hence, decrease in safety margin of tramadol.

IT 36282-47-0, Tramadol hydrochloride
(oxidation of, in pharmaceutical preparation)

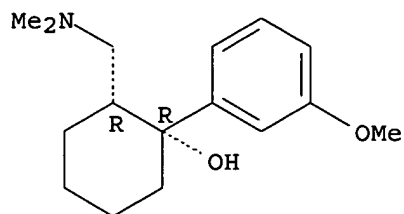
IT 147441-56-3P
(preparation of, for treatment of pain and diarrhea and tussive conditions)

IT 36282-47-0, Tramadol hydrochloride
(oxidation of, in pharmaceutical preparation)

RN 36282-47-0 USPATFULL

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● HCl

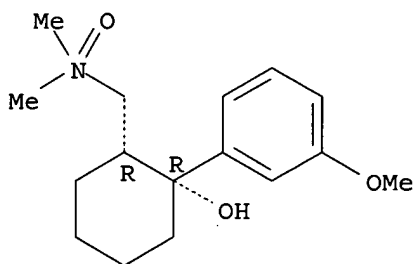
IT 147441-56-3P

(preparation of, for treatment of pain and diarrhea and tussive conditions)

RN 147441-56-3 USPATFULL

CN Cyclohexanol, 2-[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)-,
(1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L117 ANSWER 7 OF 10 USPATFULL on STN

AN 93:31188 USPATFULL

TI External preparation comprising calcium silicate

IN Shiobara, Takao, 20-18, Keyaki 1-chome, Honjo-shi, Saitama, Japan
Nonaka, Jun, 15-4, Midori 1-chome, Honjo-shi, Saitama, Japan
Kasai, Masayoshi, 156, Tsutsujigaoka 5-chome, Kakamigahara-shi, Gifu,
Japan
Konita, Takeshi, 2-2, Fukiagemachihoncho 3-chome, Kitaadachi-gun,
Saitama, Japan

PI US 5204119 19930420

AI US 1991-748208 19910820 (7) <--

PRAI JP 1990-228669 19900829 <--

DT Utility

FS Granted

EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Spear, James M.

LREP Flynn, Thiel, Boutell & Tanis

CLMN Number of Claims: 7

ECL Exemplary Claim: 1

DRWN 7 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 453

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB An external preparation is characterized by comprising calcium silicate.
The calcium silicate controls the release rate and percutaneous
absorbability of a drug.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AI US 1991-748208 19910820 (7) <--

PRAI JP 1990-228669 19900829 <--

SUMM Indomethacin, ketoprofen, flurbiprofen, **acetaminophen**,
 alclofenac, perisoxal citrate, sulidanac, sulpyrine, aluminum
 flufenamate, **tramadol** hydrochloride, sulindac, pentazocine,
 fentiazac, tolmetin sodium, naproxen, fenbufen, pranoprofen, piroxicam,
 clofezone, pentazocine, dichlofenac sodium, mepirizole, aspirin, aspirin
 aluminum, acemetacin, amfenac. . .

L117 ANSWER 8 OF 10 USPATFULL on STN

AN 91:102048 USPATFULL
 TI Continuous preparation of solid pharmaceutical forms
 IN Klimesch, Roger, Alsbach-Haehnlein, Germany, Federal Republic of
 Bleckmann, Gerhard, Lampertheim, Germany, Federal Republic of
 Farwerck, Karl-Peter, Worms, Germany, Federal Republic of
 Schlemmer, Lothar, Maxdorf, Germany, Federal Republic of
 Sanner, Axel, Frankenthal, Germany, Federal Republic of
 PA BASF Aktiengesellschaft, Ludwigshafen, Germany, Federal Republic of
 (non-U.S. corporation)
 PI US 5073379 19911217 <--
 AI US 1989-398663 19890825 (7) <--
 DCD 20060131
 PRAI DE 1988-3830353 19880907 <--
 DT Utility
 FS Granted
 EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Spear, James M.
 LREP Oblon, Spivak, McClelland, Maier & Neustadt
 CLMN Number of Claims: 20
 ECL Exemplary Claim: 1
 DRWN 6 Drawing Figure(s); 3 Drawing Page(s)
 LN.CNT 813
 AB A mixture of one or more pharmaceutical active compounds and one or more
 thermoplastic polymers is tabletted by a process in which the mixture is
 extruded and the still moldable extrudate is pressed to give tablets,
 between two belts, or a belt and a roller, which make contact in parts,
 rotate in opposite directions and run parallel along the contact zone,
 the shape-imparting indentations, which may be present in complementary
 pairs, being located in both or in only one of the revolving
 shape-imparting elements.

PI US 5073379 19911217 <--
 AI US 1989-398663 19890825 (7) <--
 PRAI DE 1988-3830353 19880907 <--
 SUMM . . . amitriptyline, diclofenac, nifedipine, verapamil, pyritinol,
 nitrendipine, doxycycline, bromhexin, methylprednisolone, clonidine,
 fenofibrate, allopurinol, pirenzepine, levothyroxine, tamoxifen,
 metildigoxin, o-(β -hydroxyethyl)-rutoside, propicillin, acyclovir
 mononitrate, **paracetamol**, naftidrofuryl, pentoxifylline,
 propafenone, acebutolol, L-thyroxine, **tramadol**, bromocriptine,
 loperamide, ketotifen, fenoterol, Ca dobelisate, propranolol,
 minocycline, nicergoline, ambroxol, metoprolol, β -sitosterine,
 enalapril hydrogen maleate, bezafibrate, ISDN, gallopamil, xanthinol
 nicotinate, . . .

SUMM Solid solutions of the following active compounds are particularly
 preferred: **acetaminophen** (=paracetamol),
 acetohexamide, acetyldigoxin, acetylsalicylic acid, acromycin, anipamil,
 benzocaine, β -carotene, chloramphenicol, chlordiazepoxide,
 chlormadinone acetate, chlorothiazide, cinnarizine, clonazepam, codeine,
 dexamethasone, diazepam, dicumarol, digitoxin, . . .

DETD . . . Benzocaine A 30

30

40 50

60

70

70

					10
46	5,5-Diphenhydramine				
	A	60			
		80			
		100			
		120			
		120			
		120			
		130			
		10			
47	Paracetamol				
	A	60			
		80			
		100			
		120			
		120			
		120			
		130			
		10			
48	Sulfathiazole				
	A	70			
		90			
		100			
		100			
		100			
		100			
		130			
		10			

49 Vitamin. . .

CLM What is claimed is:

. . . 15. A process as claimed in claim 14, wherein one or more active compounds from the following group are used: **acetaminophen** (= **paracetamol**), acetohexamide, acetyldigoxin, acetylsalicylic acid, acromycin, anipamil, benzocaine, β -carotene, chloramphenicol, chlordiazepoxide, chlormadinone acetate, chlorothiazide, cinnarizine, clonazepam, codeine, dexamethasone, diazepam, dircumarol, digitoxin, . . .

L117 ANSWER 9 OF 10 USPATFULL on STN

AN 89:7426 USPATFULL

TI Preparation of solid pharmaceutical forms

IN Goertz, Hans-Helmut, Freinsheim, Germany, Federal Republic of
Klimesch, Roger G., Alsbach-Haehnlein, Germany, Federal Republic of
Laemmerhirt, Klaus, Boehl-Iggelheim, Germany, Federal Republic of
Lang, Siegfried, Ludwigshafen, Germany, Federal Republic of
Sanner, Axel, Frankenthal, Germany, Federal Republic of
Spengler, Reinhard, Ludwigshafen, Germany, Federal Republic of
PA BASF Aktiengesellschaft, Germany, Federal Republic of (non-U.S. corporation)

PI US 4801460 19890131 <--

AI US 1987-34938 19870406 (7) <--

PRAI DE 1986-3612212 19860411 <--

DT Utility

FS Granted

EXNAM Primary Examiner: Lusignan, Michael

LREP Keil & Weinkauff

CLMN Number of Claims: 9

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 601

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Process for the preparation of solid pharmaceutical forms by mixing one or more pharmaceutical active compounds with one or more fusible,

pharmacologically tolerated binders and, if required, other conventional pharmaceutical auxiliaries, at from 50° to 180° C., and subjecting the mixture to injection molding or extrusion and shaping, wherein the fusible binder used is a NVP polymer which contains not less than 20% by weight of NVP as copolymerized units, and, where they are present, all of whose comonomers contain nitrogen and/or oxygen.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 4801460 19890131 <--
 AI US 1987-34938 19870406 (7) <--
 PRAI DE 1986-3612212 19860411 <--
 SUMM . . . amitriptylin, diclofenac, nifedipine, verapamil, pyritinol, nitrendipin, doxycycline, bromhexine, methylprednisolone, clonidine, fenofibrate, allopurinol, pirenzepine, levothyroxin, tamoxifen, metildigoxin, o-(β-hydroxyethyl)-rutoside, propicillin, aciclovir mononitrate, **paracetamol**, naftidrofuryl, pentoxifylline, propafenone, acebutolol, L-thyroxin, **tramadol**, bromocriptine, loperamide, ketotifen, fenoterol, cadobelisate, propanolol, enalaprilhydrogen maleate, bezafibrate, ISDN, gallopamil, xantinol nicotinate, digitoxin, flunitrazepam, bencyclane, dexapanthenol, pindolol, lorazepam, diltiazem, . . .
 SUMM Solid solutions of the following active compounds are particularly preferred: **acetaminophen (paracetamol)**, acetohexamide, acetyldigoxin, acetylsalicylic acid, acromycin, anipamil, benzocaine, β-carotene, chloramphenicol, chlordiazepoxide, chlormadinone acetate, chlorothiazide, cinnarizine, clonazepam, codeine, dexamethasone, diazepam, dicoumarol, digitoxin, . . .
 DETD . . . Weight ratio

T1
 T2
 T3 T4 T5 T6
 °C.

17a Benzocaine	A	1:3	20						
			30						
			40	40	50	50			
							50		
18 Paracetamol	C	1:3	60						
			80						
			100						
				120					
					120				
						120			
							120		
19 Phenytoin	C	1:3	60						
			80						
			100						
				120					
					120				
						120			
							120		
20 Benzocaine	C	1:1	30						
. . . Benzocaine			30						
			40	50	50	60			
							60		
28 Phenytoin	A	1:3	60						
			80						

100
120
120
120
130

29 Paracetamol
A 1:3 60
80
100
120
120
120
130

30 Sulfathiazole
A 1:1 70
90
100
100
100
100
130

31 Benzocaine

CLM What is claimed is:

7. A process as defined in claim 1, wherein one or more active compounds from the following group are used: **acetaminophen** (**paracetamol**), acetohehexamide, acetyldigoxin, acetylsalicylic acid, acromycin, anipamil, benzocaine, β -carotene, chloramphenicol, chlordiazepoxide, chlormadinone acetate, chlorothiazide, cinnarizine, clonazepam, codeine, dexamethasone, diazepam, dicoumarol, digitoxin,.

L117 ANSWER 10 OF 10 USPATFULL on STN

AN 89:7424 USPATFULL
TI Sustained release pharmaceutical plaster
IN Hidaka, Osafumi, Tokyo, Japan
Sakai, Tomoki, Tokyo, Japan
Sakano, Toyoaki, Tokyo, Japan
PA Teijin Limited, Osaka, Japan (non-U.S. corporation)
PI US 4801458 19890131 <--
WO 8700046 19870115 <--
AI US 1987-17946 19870224 (7) <--
WO 1986-JP317 19860623 <--
19870224 PCT 371 date
19870224 PCT 102(e) date
PRAI JP 1985-135917 19850624 <--
DT Utility
FS Granted
EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Horne, L. R.
LREP Sughrue, Mion, Zinn, Macpeak & Seas
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 1055
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A sustained release pharmaceutical plaster which is characterized in that it is a pharmaceutical preparation mainly composed of an adhesive compound layer and a supporter which supports the adhesive compound layer, inside of which there is an arrangement of hollow fibers, that have radially arranged open pores, with their tubular hollows filled with medicines.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 4801458 19890131 <--
WO 8700046 19870115 <--
AI US 1987-17946 19870224 (7) <--
WO 1986-JP317 19860623 <--
19870224 PCT 371 date
19870224 PCT 102(e) date
PRAI JP 1985-135917 19850624 <--
DETD . . . salicylamide, glycol salicylate, l-menthol, aminopyrine,
antipyrine, clofezone, ketophenylbutazone, camphor, mentha oil, thymol,
isopropylantipyrine, phenylbutazone, feprazone, bezyl nicotimate ester,
capsicum extract, capsaicin, **acetaminophen**, oxyphenbutazone,
pentazocine, eptazocine, diffunisal, phenazole, mepirizole, piroxicam,
benzylamine, phenacetin, tiaramide, bufexamac, flufenamic acid, aluminum
flufenamate, indometacin, **tramadol** hydrochloride, ibuprofen,
acemetacin, sulpyrine, guaiazulene, ketoprofen, flurbiprofen, diclofenac
sodium, fenoprofen, naproxen, clidanac, sulindac, benoxabrofen,
indoprofen, mefenamic acid, tolmetin, metiazinic acid, . . .

=> => fil biosis

FILE 'BIOSIS' ENTERED AT 08:53:01 ON 06 APR 2005

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FILE COVERS 1969 TO DATE.

CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 1 April 2005 (20050401/ED)

FILE RELOADED: 19 October 2003.

=> d 1167 all tot

L167 ANSWER 1 OF 2 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 1991:353490 BIOSIS
DN PREV199141038005; BR41:38005
TI ANALGESIC ORAL EFFICACY OF **TRAMADOL** HYDROCHLORIDE IN PAIN
FOLLOWING CESAREAN SECTION.
AU SUNSHINE A [Reprint author]; ZIGHELBOIM I; OLSON N Z; DECASTRO A; MINN F L
CS NYU MED CENT, NEW YORK, NY, USA
SO Clinical Pharmacology and Therapeutics, (1991) Vol. 49, No. 2, pp. 181.
Meeting Info.: NINETY-SECOND ANNUAL MEETING OF THE AMERICAN SOCIETY FOR
CLINICAL PHARMACOLOGY AND THERAPEUTICS, SAN ANTONIO, TEXAS, USA, MARCH
13-15, 1991. CLIN PHARMACOL THER.
CODEN: CLPTAT. ISSN: 0009-9236.
DT Conference; (Meeting)
FS BR
LA ENGLISH
ED Entered STN: 1 Aug 1991
Last Updated on STN: 11 Sep 1991
CC General biology - Symposia, transactions and proc
Biochemistry studies - General 10060
Anatomy and Histology - Surgery 11105
Pathology - Therapy 12512
Reproductive system - General and methods 16501
Nervous system - Pathology 20506
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Clinical pharmacology 22005
Pharmacology - Neuropharmacology 22024
Toxicology - Pharmacology 22504
IT Major Concepts

*No Abstracts -
Relevance depends
on full-text
Publication*

Nervous System (Neural Coordination); Pharmacology; Reproductive System
(Reproduction); Surgery (Medical Sciences)

IT Miscellaneous Descriptors
ABSTRACT HUMAN **ACETAMINOPHEN** ANALGESIC-DRUG NO ADVERSE
EFFECTS PHARMACOKINETICS

RN 36282-47-0 (**TRAMADOL** HYDROCHLORIDE)
103-90-2 (**ACETAMINOPHEN**)

L167 ANSWER 2 OF 2 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 1986:247721 BIOSIS
DN PREV198631002433; BR31:2433
TI ANALGESICS IN DENTAL PRACTICE.
AU HOTZ G [Reprint author]
CS ABTEILUNG FUER ZAHNAERZTLICHE-UND KIEFERCHIRURGIE, ZZMK, HOSPITALSTRASSE
1, D-6900 HEIDELBERG 1
SO ZWR (Heidelberg), (1985) Vol. 94, No. 11, pp. 892-896.
CODEN: ZWRSBR. ISSN: 0044-166X.
DT Article
FS BR
LA GERMAN
ED Entered STN: 13 Jun 1986
Last Updated on STN: 13 Jun 1986
CC Biochemistry studies - General 10060
Pathology - Therapy 12512
Dental biology - General and methods 19001
Pharmacology - Clinical pharmacology 22005
Pharmacology - Neuropharmacology 22024
IT Major Concepts
Dental and Oral System (Ingestion and Assimilation); Pharmacology
IT Miscellaneous Descriptors
HUMAN **PARACETAMOL** PHENACETIN PROPYPHENAZONE CAFFEINE CODEIN
PHOSPHATE BUTALBITAL SALICYLAMIDE BUPRENORPHINE DEXTROMORAMIDE
HYDROMORPHONE LEVO METHADONE MORPHINE PENTAZOCINE **PARACETAMOL**
PETHIDINE PIRITRAMIDE CODEINE DIHYDROCODEINE DEXTROPROPOXYPHENE NEFOPAM
NALOXONE TILIDINE **TRAMADOL** ANALGESIC-DRUG

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 103-90-2 (**PARACETAMOL**)
62-44-2 (PHENACETIN)
58-08-2 (CAFFEINE)
14265-44-2 (PHOSPHATE)
77-26-9 (BUTALBITAL)
65-45-2 (SALICYLAMIDE)
52485-79-7 (BUPRENORPHINE)
357-56-2 (DEXTROMORAMIDE)
466-99-9 (HYDROMORPHONE)
125-58-6 (LEVO-METHADONE)
57-27-2 (MORPHINE)
359-83-1 (PENTAZOCINE)
57-42-1 (PETHIDINE)
302-41-0 (PIRITRAMIDE)
76-57-3 (CODEINE)
125-28-0 (DIHYDROCODEINE)
469-62-5 (DEXTROPROPOXYPHENE)
13669-70-0 (NEFOPAM)
465-65-6 (NALOXONE)
51931-66-9 (TILIDINE)
27203-92-5 (**TRAMADOL**)
20380-58-9 (TILIDINE)

=> d his

(FILE 'HOME' ENTERED AT 07:06:24 ON 06 APR 2005)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 07:06:33 ON 06 APR 2005

E TRAMADOL/CN
L1 1 S E3
E C16H25NO2/MF
L2 149 S E3 AND (46.150.18 AND 46.150.1)/RID
L3 4 S L2 AND TRAMADOL
L4 29 S L2 AND CYCLOHEXANOL AND DIMETHYLAMINO AND METHOXYPHENYL
L5 25 S L4 NOT L1,L3
L6 13 S L5 AND 3 METHOXYPHENYL
SEL RN 4 5 13
L7 3 S E1-E3
L8 7 S L1,L3,L7
SEL RN
L9 71 S E4-E10/CRN
E ACETAMINOPHEN/CN
L10 1 S E3
L11 395 S C8H9NO2/MF AND 46.150.18/RID AND 1/NR
L12 66 S L11 AND HYDROXYPHENYL
L13 36 S L12 AND ACETAMIDE
L14 24 S L13 AND 4
L15 1 S L10 AND L14
SEL RN
L16 325 S E1/CRN
L17 2 S L9 AND L16
L18 69 S L9 NOT L17
L19 43 S L18 AND (MXS/CI OR COMPD OR WITH)
L20 26 S L18 NOT L19
L21 301 S L16 AND (MXS/CI OR COMPD OR WITH)
L22 2 S L21 AND C16H25NO2
L23 2 S L17,L22
L24 24 S L16 NOT L21

FILE 'HCAPLUS' ENTERED AT 07:23:11 ON 06 APR 2005

L25 15 S L23
L26 2 S L25 AND (RAFFA R? OR VAUGHT J?)/AU
L27 1 S L25 AND (ORTHO? OR MCNEIL? OR MC NEIL?)/PA,CS
L28 1 S L25 AND (PY<=1991 OR PRY<=1991 OR AY<=1991)
L29 2 S L26-L28
L30 1058 S L8 OR L20
L31 1144 S TRAMADOL OR U26255A OR U() (26255A OR 26255 A OR 26 255A OR 26
L32 17 S 2 DIMETHYLAMINO METHYL 1 3 METHOXYPHENYL CYCLOHEXANOL
L33 1 S 2() (DIMETHYL OR DIMETHYL OR DI METHYL OR DIME)()AMINO METHYL
L34 45 S TRAMAL OR CG315 OR CG 315
L35 1198 S L30-L34
L36 11440 S L15 OR L24
L37 7018 S ACETAMINOPHEN? OR TYLENOL
L38 98 S (4 OR P OR PARA)() (HYDROXYPHENYL OR HYDROXY PHENYL)()ACETAMID
L39 4876 S PARACETAMOL
L40 15 S 4() (ACETYLAMINO OR ACETYL AMINO)()PHENOL
L41 463 S (4 OR P)()ACETAMIDOPHENOL
L42 404 S (4 OR P)() (HYDROXYACETANILIDE OR HYDROXY ACETANILIDE)
L43 63 S ABENSANIL OR ACAMOL OR ACENOL OR ACETAGESIC OR ACETALGIN OR A
L44 368 S CLARATAL OR CLIXODYNE OR CROCIN# OR DAFALGAN# OR DAPHALGAN# O
L45 175 S FEBROGESIC OR FEBRO GESIC OR FEBROLIN# OR FENDON# OR FEPANIL#
L46 4951 S NEBS OR NOBEDON# OR NSC109028 OR NSC() (109028 OR 109 028) OR
L47 990 S PARALEN# OR PARAMOL? OR PARASPEN# OR PARELAN# OR PARMOL OR PA

L48 8 S TABALGIN# OR TACHIPIRINA OR TAPAR OR TEMLO OR TEMPANAL OR TEM
L49 11 S ACETYL(1W) (HYDROXYANILINE OR HYDROXY ANILINE)
L50 327 S ACETYLAMINOPHENOL OR ACETYL AMINOPHENOL OR ACETYL AMINO PHENO
L51 1563 S ACETANILIDE(L)HYDROXY
L52 372 S ACETYL(1W) (AMINOPHENOL OR AMINO PHENOL)
L53 16899 S L36-L52
L54 201 S L35 AND L53
L55 6 S L54 AND (RAFFA ? OR VAUGHT ?)/AU
L56 5 S L54 AND (ORTHO? OR MCNEIL? OR MC NEIL?)/PA,CS
L57 9 S L55,L56
L58 8 S L57 NOT PSOAS/TI
L59 12 S L54 AND (PY<=1991 OR PRY<=1991 OR AY<=1991)
L60 10 S L59 NOT L29,L58
SEL DN AN 1 2
L61 2 S L60 AND E2-E7
L62 10 S L29,L58,L61
L63 10 S L62 AND L25-L62
L64 4 S L63 AND TRAMADOL(S) (HCL OR HYDROCHLORIDE)
L65 10 S L63,L64
SEL RN

FILE 'REGISTRY' ENTERED AT 07:51:18 ON 06 APR 2005

L66 192 S E8-E199
L67 2 S L66 AND L23
L68 6 S L66 AND L8,L9
L69 17 S L66 AND L15,L16
L70 10 S L66 AND L24
L71 6 S L69 NOT L15,L70
L72 5 S L71 NOT 330988-71-1
L73 19 S L67,L68,L70,L72
L74 173 S L66 NOT L73
L75 8 S L74 AND (46.150.18 AND 46.150.1)/RID
SEL RN 2-6
L76 5 S E200-E204
L77 24 S L73,L76

FILE 'HCAPLUS' ENTERED AT 07:57:05 ON 06 APR 2005

L78 10 S L77 AND L65
L79 94 S L76
L80 1124 S ?TRAMADOL?
L81 194 S L79,L80 AND L53
L82 10 S L81 AND (PY<=1991 OR PRY<=1991 OR AY<=1991)
L83 6 S L82 NOT L78
L84 10 S L78 AND L25-L65,L78-L83
SEL HIT RN

FILE 'REGISTRY' ENTERED AT 07:58:51 ON 06 APR 2005

L85 25 S E205-E229

FILE 'REGISTRY' ENTERED AT 07:59:12 ON 06 APR 2005

L86 6 S L8 NOT L85

FILE 'HCAPLUS' ENTERED AT 08:00:31 ON 06 APR 2005

FILE 'WPIX' ENTERED AT 08:03:06 ON 06 APR 2005

L87 335 S L31/BIX OR L32/BIX OR L33/BIX OR L34/BIX
E TRAMADOL/DCN
E E3+ALL
L88 267 S E2
E TRAMADOL/CN
L89 7 S E4-E13
L90 50 S (RAF613 OR RA4BD7 OR RA0HAR OR RAOHAR OR RAOHAF OR RAOHAF OR
L91 364 S L87,L88,L90

L92 2169 S L37/BIX OR L38/BIX OR L39/BIX OR L40/BIX OR L41/BIX OR L42/BI
E ACETAMINOPHEN/DCN
E E3+ALL
L93 1338 S E2 OR 0758/DRN
L94 646 S E4
E ACETAMINOPHEN/CN
L95 2587 S L92-L94
L96 71 S L91 AND L95
L97 3 S L96 AND (RAFFA ? OR VAUGHT ?)/AU
L98 4 S L96 AND (MCNEIL? OR MC NEIL? OR ORTHO?)/PA,CS
L99 4 S L97,L98
E 9312-29401/DCN
L100 1 S E3,E4
L101 4 S L99,L100
L102 67 S L96 NOT L101
L103 0 S L102 AND (PY<=1991 OR PRY<=1991 OR AY<=1991)
L104 3279 S L95 OR A61K031-167/IPC
L105 75 S L104 AND L91
L106 4 S L105 NOT L96
L107 4 S L101 AND L87-L106

FILE 'WPIX' ENTERED AT 08:21:24 ON 06 APR 2005

FILE 'USPATFULL' ENTERED AT 08:21:55 ON 06 APR 2005

L108 1267 S L35
L109 12423 S L53
L110 0 S L23
L111 562 S L108 AND L109
L112 6 S L111 AND (RAFFA ? OR VAUGHT ?)/AU
L113 6 S L85 AND L112
L114 151 S L85 AND L111
L115 556 S L111,L114 NOT L113
L116 4 S L115 AND (PY<=1991 OR PRY<=1991 OR AY<=1991)
L117 10 S L113,L116 AND L108-L116

FILE 'USPATFULL' ENTERED AT 08:26:20 ON 06 APR 2005

FILE 'DRUGU' ENTERED AT 08:27:30 ON 06 APR 2005

L118 1229 S L31-L34
L119 14638 S L37-L52
L120 318 S L118 AND L119
L121 44 S L120 AND PY<=1991

FILE 'PS' ENTERED AT 08:34:43 ON 06 APR 2005

L122 1 S L31-L34 OR ?TRAMADOL?

FILE 'DDFB' ENTERED AT 08:35:59 ON 06 APR 2005

L123 52 S L31-L34
L124 3497 S L37-L52
L125 4 S L123 AND L124

FILE 'EMBASE' ENTERED AT 08:38:10 ON 06 APR 2005

L126 3560 S L31-L34 OR ?TRAMADOL?
L127 0 S L23
L128 3519 S L8 OR L20
L129 3560 S L126,L128
L130 30205 S L37-L52
L131 28444 S L15 OR L24
L132 30205 S L130,L131
L133 1118 S L129 AND L132
L134 58 S L133 AND PY<=1991
L135 456 S (TRAMADOL(L)CB)/CT
L136 2569 S (PARACETAMOL(L)CB)/CT

L137 1 S L134 AND L135
L138 0 S L134 AND L136
L139 57 S L134 NOT L137
L140 47 S L139 NOT AB/FA
L141 10 S L139 NOT L140
L142 0 S L140 AND SYNERG?

FILE 'CANCERLIT' ENTERED AT 08:44:22 ON 06 APR 2005

L143 0 S L23
L144 43 S L8 OR L20
L145 55 S L31-L34 OR ?TRAMADOL?
L146 55 S L144,L145
L147 430 S L15 OR L24
L148 863 S L37-L52
L149 863 S L147,L148
L150 4 S L146 AND L149

FILE 'MEDLINE' ENTERED AT 08:45:51 ON 06 APR 2005

L151 0 S L23
L152 874 S L8 OR L20
L153 1128 S L31-L34 OR ?TRAMADOL?
L154 1128 S L152,L153
L155 8849 S L15 OR L24
L156 11998 S L37-L52
L157 11998 S L155,L156
L158 136 S L154 AND L157
L159 1 S L158 AND PY<=1991

FILE 'BIOSIS' ENTERED AT 08:47:59 ON 06 APR 2005

E RAFFA R/AU
L160 179 S E3,E5,E7,E9
E VAUGHT J/AU
L161 173 S E3,E7,E9-E13
L162 0 S L23
L163 1095 S L8 OR L20 OR L31-L34 OR ?TRAMADOL?
L164 11900 S L15 OR L24 OR L37-L52
L165 98 S L163 AND L164
L166 5 S L165 AND PY<=1991
SEL DN AN 1 5
L167 2 S L166 AND E1-E6
L168 31 S L160,L161 AND L163,L164
L169 3 S L168 AND L165
L170 28 S L168 NOT L169

FILE 'BIOSIS' ENTERED AT 08:53:01 ON 06 APR 2005

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